femhrt®

(norethindrone acetate/ethinyl estradiol tablets)

WARNING

Estrogens and progestins should not be used for the prevention of cardiovascular disease.

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 during 5 years of treatment with conjugated equine estrogens (CE 0.625 mg) combined with 2.5mg medroxyprogesterone acetate (MPA 2.5 mg) relative to placebo (see **WARNINGS**).

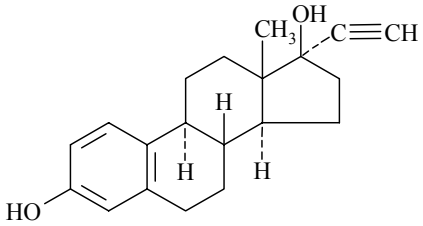
Other doses of conjugated estrogens with medroxyprogesterone, and other combinations of estrogens and progestins were not studied in the WHI and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

DESCRIPTION

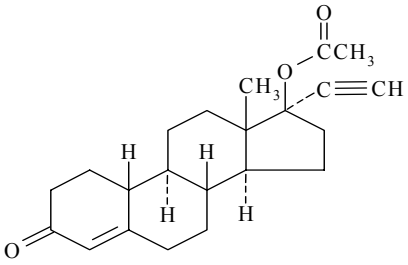
femhrt® 1/5 is a continuous dosage regimen of a progestin-estrogen combination for oral administration.

Each white D-shaped tablet contains 1 **mg** norethindrone acetate [19-Norpregn-4-en-20-yn-3-one, 17-(acetyloxy)-, (17α)-] and 5 **mcg** ethinyl estradiol [19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)-]. Each tablet also contains calcium stearate, lactose monohydrate, microcrystalline cellulose, and cornstarch.

The structural formulas are as follows:



Ethinyl Estradiol
Molecular Weight: 296.41
Molecular Formula: $C_{20}H_{24}O_2$



Norethindrone Acetate
Molecular Weight: 340.47
Molecular Formula: $C_{22}H_{28}O_3$

CLINICAL PHARMACOLOGY

Estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sex 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 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 sulphate conjugated form, estrone sulphate, are the most abundant circulating estrogens in postmenopausal women. The pharmacologic effects of ethinyl estradiol are similar to those of endogenous estrogens.

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.

The use of unopposed estrogen therapy has been associated with an increased risk of endometrial hyperplasia, a possible precursor of endometrial adenocarcinoma. The addition of continuous administration of progestin to an estrogen regimen reduced the incidence of endometrial hyperplasia, and the attendant risk of carcinoma in women with intact uteri.

Pharmacokinetics

Absorption and Bioavailability
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* 1/5 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* 1/5 tablets is similar to that from solution for norethindrone and slightly less for ethinyl estradiol. Administration of norethindrone acetate/ethinyl estradiol (NA/EE) 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 NA/EE tablets with food.

The full pharmacokinetic profile of *femhrt* 1/5 (1 **mg** norethindrone acetate/5 **mcg** ethinyl estradiol) 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 0.5 **mg** NA/2.5 **mcg** EE 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

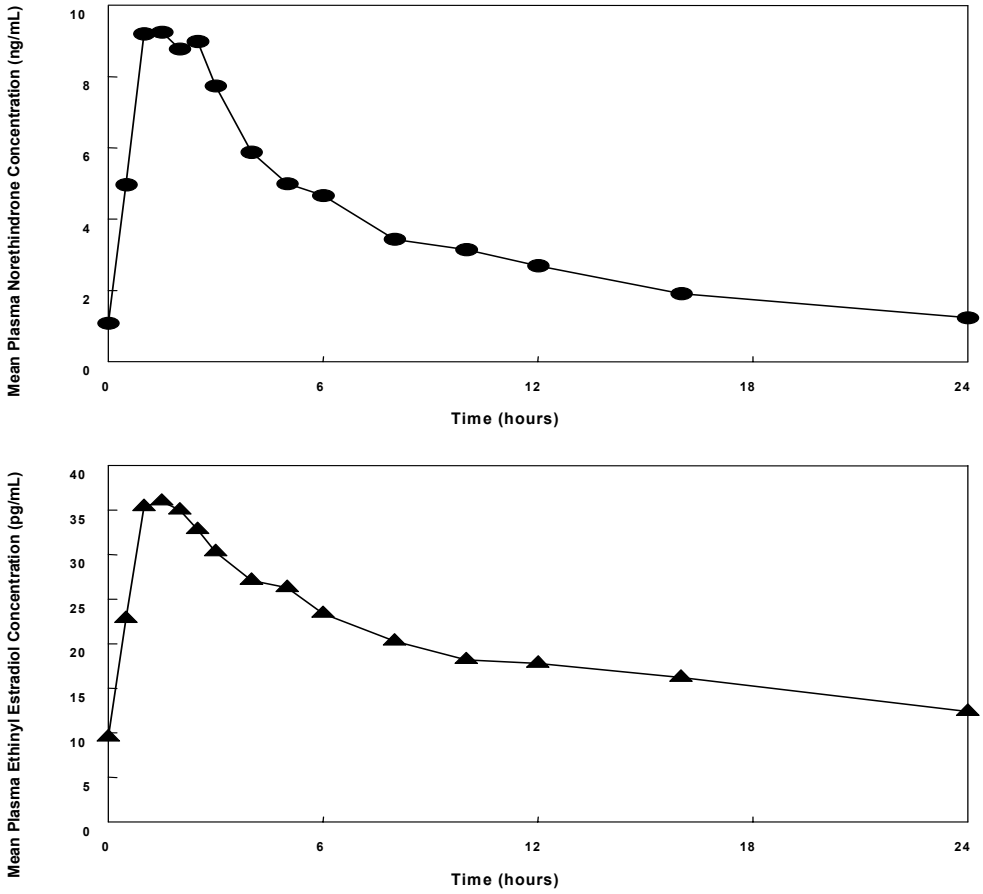


Table 1. Mean (SD) Single-Dose (Day 1) and Steady-State (Day 87) Pharmacokinetic Parameters[a] Following Administration of 1 mg NA/10 mcg EE Tablets

	C_{max}	t_{max}	AUC(0-24)	CL/F	$t_{½}$
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)

[a] C_{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; $t_{½}$ = Elimination half-life

[b] ND=Not determined

Based on a population pharmacokinetic analysis, average steady-state concentrations (Css) of norethindrone and ethinyl estradiol for *femhrt* 1/5 (1 **mg** NA/5 **mcg** EE) tablets are estimated to be 2.6 ng/mL and 11.4 pg/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

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

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

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 1/5 is not indicated in children.

Geriatrics

The pharmacokinetics of *femhrt* 1/5 have not been studied in a geriatric population.

Race

The effect of race on the pharmacokinetics of *femhrt* 1/5 has not been studied.

Patients with Renal Insufficiency

The effect of renal disease on the disposition of *femhrt* 1/5 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* 1/5 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.**

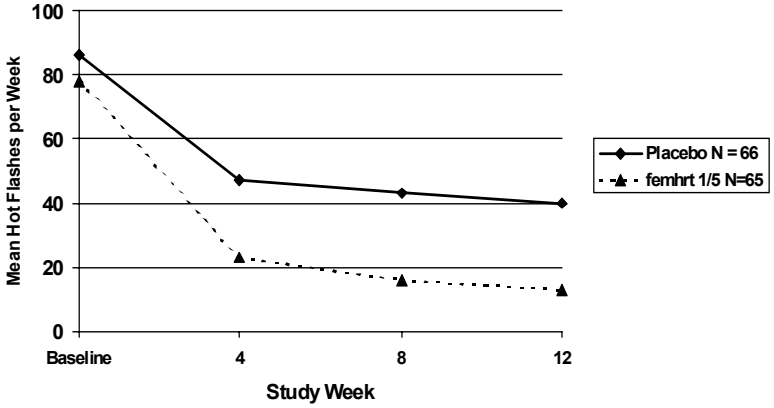
Clinical Studies

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 flashes during the week prior to randomization. On average, patients had 12 hot flashes per day upon study entry.

A total of 65 women were randomized to receive *femhrt* 1/5 and 66 women were randomized to the placebo group. The efficacy of *femhrt* 1/5 for the treatment of moderate to severe vasomotor symptoms (VMS) is demonstrated in Figure 2.

Figure 2: Mean Hot Flash Frequencies by Treatment Group: Baseline Through Week 12 (Intent-to-Treat-Population, Last Observation Carried Forward)



Endometrial Hyperplasia

A 2-year, placebo-controlled, multicenter, randomized clinical trial was conducted to determine the safety and efficacy of *femhrt* 1/5 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, 0.5 **mg** NA/2.5 **mcg** EE, *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, and 141 to EE 5 **mcg**. Of these, 134 placebo, 143 *femhrt* 1/5, and 139 EE 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 2.

Table 2. Endometrial Biopsy Results After 12 and 24 Months of Treatment

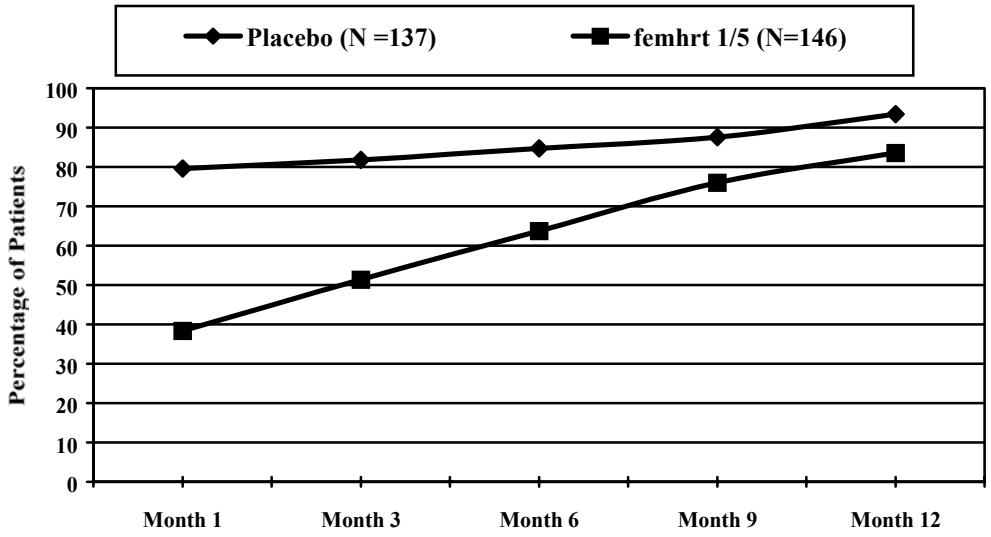
Number of Patients Biopsied at Baseline	Placebo N= 134	*femhrt* 1/5 N= 143	5 mcg ethinyl estradiol N=139
MONTH 12			
Patients Biopsied (%)	113 (84)	110 (77)	114 (82)
Insufficient Tissue	30	45	20
Atrophic Tissue	60	41	2
Proliferative Tissue	23	24	91
Endometrial Hyperplasia[a]	0	0	1
MONTH 24			
Patients Biopsied (%)	94 (70)	102 (71)	107 (77)
Insufficient Tissue	35	37	17
Atrophic Tissue	38	33	2
Proliferative Tissue	20	32	86
Endometrial Hyperplasia[a]	1	0	2

[a]All 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, was evaluated over 12 months for *femhrt* 1/5 and placebo arms. Results are shown in Figure 3.

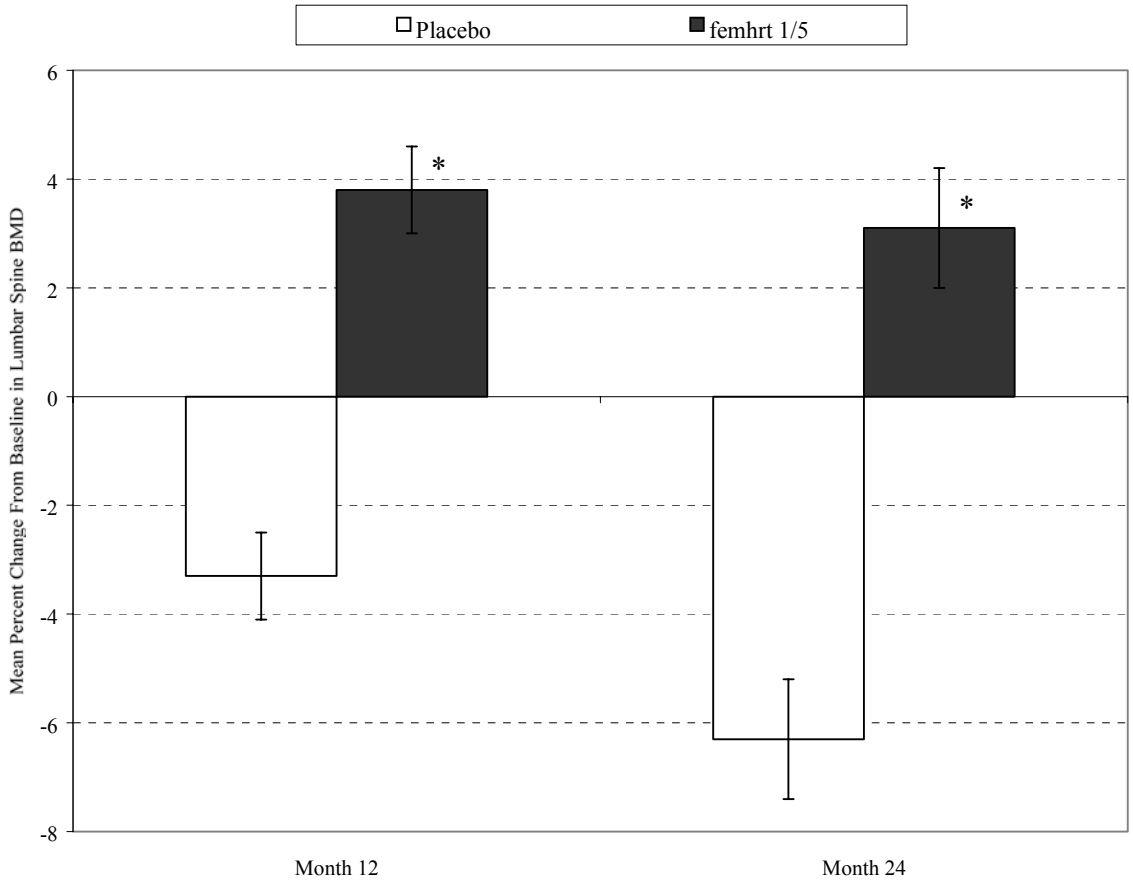
Figure 3. Patients With Cumulative Amenorrhea Over Time: Intent-To-Treat Population, Last Observation Carried Forward



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 283 postmenopausal women with intact uteri and normal baseline bone mineral density (124.14 mg/cc ± 9.60 mg/cc) were randomized to *femhrt* 1/5 (1 **mg** norethindrone acetate/5 **mcg** ethinyl estradiol) or placebo, and 87% contributed data to the Intent-To-Treat analysis. All patients received 1000 mg calcium in divided doses. Vitamin D was not supplemented. *femhrt* 1/5 resulted in significant increases in BMD at each assessment. There was a significant decrease in BMD in the placebo group (see Figure 4).

Figure 4. Mean Percent Change (± SE) From Baseline in Lumbar Spine BMD at Months 12 and 24 (Intent-to-Treat Population)



* Mean percent changes in BMD statistically significantly more positive than mean percent changes in placebo group at each time point.

INDICATIONS AND USAGE

femhrt 1/5 is indicated in women with an intact uterus for the:

1. Treatment of moderate to severe vasomotor symptoms associated with 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 and non-estrogen medications should be carefully considered.

Since estrogen administration is associated with risks as well as benefits, selection of patients ideally should be based on prospective identification of risk factors for developing osteoporosis. Unfortunately, there is no certain way to identify those women who will develop osteoporotic fractures. Thus, patient selection must be individualized based on the balance of risks and benefits.

Estrogen therapy reduces bone resorption and retards or halts postmenopausal bone loss. Case-control studies have shown an approximately 60% reduction in hip and wrist fractures in women whose estrogen therapy was begun within a few years of menopause. Studies also suggest that estrogen reduces the rate of vertebral fractures. Even when started as late as 6 years after menopause, estrogen may prevent further loss of bone mass for as long as the treatment is continued. When estrogen therapy is discontinued, bone mass declines at a rate comparable to that in the immediate postmenopausal period. There is no evidence that estrogen therapy restores bone mass to premenopausal levels.

Early menopause is one of the strongest predictors for the development of osteoporosis.

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 1500mg/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.

CONTRAINDICATIONS

Progestogens/estrogens should not be used in individuals with any of the following conditions or circumstances:

1. Known or suspected pregnancy. There is no indication for *femhrt* 1/5 in pregnancy. There appears to be little or no increased risk of birth defects in women who have used estrogens and progestins from oral contraceptives inadvertently during early pregnancy (See **PRECAUTIONS**).
2. Known, suspected, or history of cancer of the breast.
3. Known or suspected estrogen-dependent neoplasia.
4. Undiagnosed abnormal genital bleeding.
5. Active or past history of deep vein thrombosis, pulmonary embolism, thrombophlebitis or thromboembolic disorders.
6. Active or recent (e.g., within past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction).
7. Known sensitivity to *femhrt* 1/5 or other estrogen and progestin containing products.

WARNINGS

See BOXED WARNING.

Women's Health Initiative Studies.

A substudy of the Women's Health Initiative (WHI) enrolled a total of 16,608 predominantly healthy postmenopausal women (average age of 63 years, range 50 to 79;
83.9% White, 6.5% Black, 5.5% Hispanic) to assess the risks and benefits of the use of 0.625 mg conjugated equine estrogens (CE) 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/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, after an average follow-up of 5.2 years are presented in Table 4 below:

Table 4. RELATIVE AND ABSOLUTE RISK SEEN IN THE PREMPRO™ (conjugated estrogens/medroxyprogesterone) 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 Person-years	
CHD events	1.29 (1.02-1.63)	30	37
Non-fatal MI	*1.32 (1.02-1.72)*	*23*	*30*
CHD death	*1.18 (0.70-1.97)*	*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," absolute excess risks per 10,000 person-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 absolute risk reductions per 10,000 person-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 person-years. There was no difference between the groups in terms of all-cause mortality (See **BOXED WARNING**).

1. Cardiovascular disorders.

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 cardiovascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) should be managed appropriately.

a. Coronary heart disease and stroke

In the CE/MPA substudy of WHI, an increased risk of 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 person years). The increase in risk was observed in year one and persisted.

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 person-years). The increase in risk was observed after the first year and persisted.

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-0.625mg/2.5mg 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 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 woman-years in the CE/MPA group compared to 16 per 10,000 woman-years in the placebo group. The increase in VTE risk was observed during the first year and persisted.

Five epidemiologic studies have found an increased risk of VTE in users of estrogen therapy (ET) who did not have predisposing conditions for VTE, such as a past history of cardiovascular disease or a recent history of pregnancy, surgery, trauma, or serious illness. The increased risk was found only in current ET users; it did not persist in former users. The risk appeared to be higher in the first year of use and decreased thereafter. The findings were similar for ET alone or with added progestin and pertain to commonly used oral and transdermal doses, with a possible dose-dependent effect on risk. The studies found the VTE risk to be about one case per 10,000 women per year among women not using ET and without predisposing conditions. The risk in current ET users was increased to 2-3 cases

per 10,000 women per year.

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. Induction of Malignant Neoplasms

a. Breast Cancer

Estrogen/progestin therapy in postmenopausal women has been associated with an increased risk of breast cancer. In the CE/MPA substudy of WHI, a 26% increase of invasive breast cancer (38 vs 30 per 10,000 woman-years) after an average of 5.2 years of treatment was observed in women receiving CE/MPA compared to women receiving placebo. The increased risk of breast cancer became apparent after 4 years on CE/MPA. The women reporting prior postmenopausal use of estrogens and/or estrogen with progestins had a higher relative risk for breast cancer associated with CE/MPA than those who had never used these hormones.

Epidemiologic studies have reported an increased risk of breast cancer in association with increasing duration of postmenopausal treatment with estrogens with or without progestin. This association was reanalyzed in original data from 51 studies that involved various doses and types of estrogens, with and without progestins. In the reanalysis, an increased risk of having breast cancer diagnosed became apparent after about 5 years of continued treatment, and subsided after treatment had been discontinued for 5 years or longer. Some later studies have suggested that postmenopausal treatment with estrogens and progestin increase the risk of breast cancer more than treatment with estrogen alone.

A postmenopausal woman without a uterus who requires estrogen should receive estrogen-alone therapy, and should not be exposed unnecessarily to progestins. All postmenopausal women should receive yearly breast exams by a healthcare provider and perform monthly self-examinations. In addition, mammography examinations should be scheduled based on patient age and risk factors.

b. Endometrial Cancer

The reported endometrial cancer risk among users of unopposed estrogen is about 2- to 12-fold greater than in nonusers, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with the 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 use of 5 to 10 years or more, and this risk has been shown to persist for at least 15 years after cessation of estrogen treatment. Results from a 2-year clinical study of the effects of *femhrt* 1/5 on endometrial hyperplasia are shown in the **Clinical Studies** section of this label.

Clinical surveillance of all women taking progestin/estrogen 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 “natural” estrogens are more or less hazardous than “synthetic” estrogens at equivalent doses.

3. Gallbladder Disease

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

4. Hypercalcemia

Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If this occurs, the drugs should be stopped and appropriate measures taken to reduce the serum calcium level.

5. Visual Disturbances

Medication should be discontinued pending examination if there is a sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

PRECAUTIONS

A. General

1. 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 treatment. These include:

a. A possible increased risk of breast cancer

b. Adverse effects on lipoprotein metabolism (e.g., lowering HDL, raising LDL)

c. Impairment of glucose tolerance

2. Elevated Blood Pressure

Occasional blood pressure increases during estrogen therapy have been attributed to idiosyncratic reactions to estrogens. More often, blood pressure has remained the same or has dropped. One study showed that postmenopausal estrogen users have higher blood pressure than nonusers.

Two other studies showed slightly lower blood pressure among estrogen users compared to nonusers. Blood pressure should be monitored at regular intervals with estrogen use**.**

3. Use in Hysterectomized Women

Existing data do not support the use of the combination of progestin and estrogen in postmenopausal women without a uterus.

4. Physical Examination

A complete medical and family history should be taken prior to the initiation of *femhrt* 1/5 and annually thereafter. These examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolaou smear.

5. Fluid Retention

Progestin/estrogen therapy may cause some degree of fluid retention. Conditions which might be exacerbated by this factor, such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation.

6. Hypocalcemia

Estrogens should be used with caution in individuals with severe hypocalcemia

7. Ovarian cancer

Use of estrogen-only products, in particular for ten or more years, has been associated with an increased risk of ovarian cancer in some epidemiological studies. Other studies did not show a significant association. Data are insufficient to determine whether there is an increased risk with combined estrogen/progestin therapy in postmenopausal women.

8. Exacerbation of endometriosis

Endometriosis may be exacerbated with administration of estrogens.

9. Uterine Bleeding and Mastodynia

Certain patients may develop undesirable manifestations of estrogenic stimulation, such as abnormal uterine bleeding and mastodynia. In cases of undiagnosed abnormal uterine bleeding, adequate diagnostic measures are indicated (see **WARNINGS**).

10. Impaired Liver Function

Estrogens and progestins 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.

11. Pathology Specimens

The pathologist should be advised of progestin/estrogen therapy when relevant specimens are submitted.

12. 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.

13. Hypercoagulability

Some studies have shown that women taking estrogen therapy have hypercoagulability, primarily related to decreased antithrombin activity. This effect appears dose- and duration-dependent and is less pronounced than that associated with oral contraceptive use. Also, postmenopausal women tend to have changes in coagulation parameters at baseline compared to premenopausal women. There is some suggestion that low dose postmenopausal mestranol may increase the risk of thromboembolism, although the majority of studies (of primarily conjugated estrogen users) report no such increase. There is insufficient information on hypercoagulability in women who have had previous thromboembolic disease, therefore, *femhrt* 1/5 is contraindicated in such women.

14. Familial Hyperlipoproteinemia

Estrogen therapy may be associated with massive elevations of plasma triglycerides leading to pancreatitis and other complications in patients with familial defects of lipoprotein metabolism.

15. Depression

Patients who have a history of depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

16. Impaired Glucose Tolerance

Diabetic patients should be carefully observed while receiving progestin/estrogen therapy. The effects of *femhrt* 1/5 on glucose tolerance have not been studied.

B. Information for Patients

Physicians are advised to discuss the contents of the Patient Information leaflet with patients for whom they prescribe femhrt 1/5.

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

C. Drug/Laboratory Test Interactions

The following drug/laboratory interactions have been observed with estrogen therapy, and/or *femhrt* 1/5:

1. In a 12-week study, *femhrt* 1/5 decreased Factor VII and 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 did not change from baseline for *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.
3. Estrogen therapy may elevate other binding proteins in serum, ie, corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids, respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

   femhrt 1/5 was associated with a SHBG increase of 22%.
4. Estrogen therapy increases plasma HDL and HDL-2 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.

D. Drug/Drug Interactions

No drug-drug interaction studies have been conducted with *femhrt* 1/5.

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, intraconazole, 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* 1/5 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 (eg, 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 temazapam, salicylic acid, morphine, and clofibric acid have been noted when these drugs were administered with certain ethinyl-estradiol containing drug products (eg, oral contraceptives containing ethinyl estradiol).

E. 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 (see **BOXED WARNING, CONTRAINDICATIONS AND WARNINGS**).

F. Pregnancy

Estrogens/progestins should not be used during pregnancy (see **CONTRAINDICATIONS**).

G. Nursing Mothers

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk. 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 progestational drugs. The effect of this on the nursing infant has not been determined. Caution should be exercised when *femhrt* 1/5 is administered to nursing mothers.

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* 1/5 are shown in Table 5 below.

Table 5. All Treatment-Emergent Adverse Events
Reported at a Frequency of > 5% of Patients with *femhrt* 1/5
% of Patients

BODY SYSTEM/ Adverse Event	Placebo N = 247	*femhrt* 1/5 N = 258
BODY AS A WHOLE	40.1	39.5
Headache	14.6	18.2
Back Pain	5.3	4.7
Viral Infection	7.7	7.0
DIGESTIVE SYSTEM	24.4	33.0
Nausea and/or Vomiting	5.3	7.4
Abdominal Pain	4.5	8.1
MUSCULOSKELETAL SYSTEM	21.7	20.4
Arthralgia	6.9	5.8
Myalgia	8.5	7.8
PSYCHOBIOLOGIC FUNCTION	8.3	14.1
Nervousness	1.6	5.4
Depression	3.6	5.8
RESPIRATORY SYSTEM	37.2	35.6
Rhinitis	15.4	15.1
Sinusitis	9.7	8.1
UROGENITAL SYSTEM	25.0	40.8
Breast Pain	5.3	8.1
Urinary Tract Infection	3.2	6.2
Vaginitis	4.9	5.4

The following adverse events have been reported with estrogen and/or progestin therapy:

Cardiovascular: changes in blood pressure, cerebrovascular accidents, deep venous thrombosis, and pulmonary embolism.

Genitourinary system: changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow, breakthrough bleeding, spotting, increase in size of uterine leiomyomata, vaginal candidiasis, changes in amount of cervical secretion, pre-menstrual-like syndrome, cystitis-like syndrome.

Breasts: tenderness, enlargement, fibrocystic disease of the breast.

Gastrointestinal: cholestatic jaundice, pancreatitis, flatulence, bloating, abdominal cramps.

Skin: chloasma or melasma that may persist when drug is discontinued, erythema multiforme, erythema nodosum, hemorrhagic eruption, loss of scalp hair, hirsutism, itching, skin rash and pruritus.

CNS: headache, migraine, dizziness, chorea, insomnia.

Eyes: intolerance to contact lenses, sudden partial or complete loss of vision, proptosis, diplopia, otosclerosis.

Miscellaneous: increase or decrease in weight, reduced carbohydrate tolerance, aggravation of porphyria, changes in libido, fatigue, allergic or anaphylactoid reactions, leiomyoma, fibromyoma of the uterus, endometriosis.

OVERDOSAGE

ACUTE 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.

femhrt 1/5 therapy consists of a single tablet taken once daily.

1. For the Treatment of Vasomotor Symptoms

femhrt 1/5 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. Prevention of Osteoporosis

femhrt 1/5 should be given once daily to prevent postmenopausal osteoporosis (see **Clinical Studies: Effect on Bone Mineral Density**). Response to therapy can be assessed by measurement of bone mineral density.

HOW SUPPLIED

femhrt 1/5 tablets are white and available in the following strength and package sizes:

N 0430-0544-23	Bottle of 90 D-shaped tablets with 1 **mg** norethindrone acetate and 5 **mcg** ethinyl estradiol
N 0430-0544-14	Blister card of 28 D-shaped tablets with 1 **mg** norethindrone acetate and 5 **mcg** ethinyl estradiol

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 January 2004)

Please read this PATIENT INFORMATION before you start taking *femhrt* 1/5 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 *1/5 (a combination of estrogen and progestin hormones)?*

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

Using estrogens and progestins may increase your chances of getting heart attack, strokes, breast cancer, and blood clots. You and your healthcare provider should talk regularly about whether you still need treatment with *femhrt* 1/5.

What is *femhrt®* 1/5?

Your healthcare provider has prescribed *femhrt* 1/5, a combination of two hormones, a progestin (1 mg norethindrone acetate) and an estrogen (5 mcg ethinyl estradiol) intended for use once a day. This insert describes the major benefits and risks of your treatment, as well as how and when treatment may be taken. If you have any questions, please contact your physician, nurse or pharmacist.

femhrt 1/5 is approved for use in the following ways:

- **To reduce moderate to severe hot flashes** Estrogens are hormones produced by the ovaries of menstruating women. When a woman is between the ages of 45 and 55, the ovaries normally stop making estrogens. 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* 1/5.

- **To prevent thinning bones (osteoporosis).** Osteoporosis is a thinning of the bones that makes them weaker and allows them to break more easily. The bones of the spine, wrists, and hips may be affected by osteoporosis. If you use *femhrt* 1/5 only to prevent osteoporosis from menopause, talk with your healthcare provider about whether a different treatment or medicine without estrogens may be better for you. You and your healthcare provider should talk regularly about whether you should continue taking *femhrt* 1/5.

  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.

  Women likely to develop osteoporosis often have the following characteristics: white or Asian race, slim, cigarette smokers, and a family history of osteoporosis in a mother, sister or aunt. Women who have menopause at an earlier age, either naturally or because their ovaries were removed during an operation, are more likely to develop osteoporosis than women whose menopause happens later in life.

Who should not take *femhrt* 1/5?

femhrt 1/5 should not be taken in the following situations:

- **During pregnancy.** If you think you may be pregnant, do not take *femhrt* 1/5.
- **If you have unusual vaginal bleeding that has not been checked by your healthcare provider.** Unusual vaginal bleeding can be a warning sign of a serious condition, including cancer of the uterus, especially if bleeding happens after menopause. Your doctor must find out the cause of the bleeding to recommend the right treatment.

- **If you currently have or have had certain cancers.** Estrogens increase the risk of certain types of cancers, including cancer of the breast and uterus. If you have or had cancer, talk with your doctor about whether you should take *femhrt* 1/5.
- **If you currently have or have had blood clots.** (see "What are the possible risks and side effects of *femhrt* 1/5?").
- **If you have had a stroke or heart attack in the past year.**
- **After childbirth or when breast-feeding a baby.** *femhrt* 1/5 should not be taken to try to stop the breasts from filling with milk after a baby is born.
- **If you have had a hysterectomy (uterus removed).** *femhrt* 1/5 contains a progestin to decrease the risk of developing endometrial hyperplasia (an overgrowth of the lining of the uterus that may lead to cancer). If you do not have a uterus, you do not need a progestin, and you should not take *femhrt* 1/5.
- **If you are allergic to *femhrt* 1/5 or any of its ingredients.** See the end of this leaflet for a list of ingredients in *femhrt* 1/5.

Tell your healthcare provider:

- **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, or 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* 1/5 works. *femhrt* 1/5 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* 1/5?

Take your *femhrt* 1/5 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 take only your next regularly scheduled dose. Do not take two doses at the same time.

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* 1/5.

What are the possible risks and side effects of *femhrt* 1/5?

- **Heart Disease**. *femhrt* 1/5 should not be used to treat or prevent heart disease. Studies show that taking estrogen/progestin therapy may increase your risk of heart disease.
- **Cancer of the breast.** Studies show that taking estrogen/progestin therapy may increase your risk for getting breast cancer. You should have regular breast examinations by a health professional and examine your own breasts monthly. Ask your healthcare provider to show you how to do a breast exam yourself. If you are over 50 years of age, you should have a mammogram every year.
- **Cancer of the uterus**. *femhrt* 1/5 has estrogen and progestin in it. If you take any drug that contains estrogen, including *femhrt*, you should see your doctor for regular check-ups and report any unusual vaginal bleeding right away. Vaginal bleeding after menopause may be a warning

sign of a serious condition, including cancer of the uterus. Your doctor should identify the cause of any unusual vaginal bleeding.

The risk of cancer of the uterus increases when estrogens are used without a progestin. The risk also increases the longer estrogens are taken and the larger the doses. You are more likely to get cancer of the uterus if you are overweight, diabetic, or have high blood pressure. *femhrt* 1/5, which contains a progestin, reduces the estrogen-related risk of getting a condition of the uterine lining called endometrial hyperplasia. This condition may lead to cancer of the uterus (see "Other Information").

- **Gallbladder disease.** Women who use estrogens after menopause are more likely to develop gallbladder disease that leads to surgery than women who do not use estrogens.
- **Abnormal blood clotting.** Taking estrogens may cause changes in your blood clotting system that allow the blood to clot more easily. If blood clots form in your bloodstream, they can cut off the blood supply to vital organs, causing serious problems. These problems may include a stroke (by cutting off blood to the brain), a heart attack (by cutting of blood to the heart), or a pulmonary embolus (by cutting off blood supply to the lungs). Any of these conditions may cause death or serious long-term disability.
- **Vaginal bleeding.** With femhrt 1/5, menstrual-like vaginal bleeding may occur. If bleeding occurs, it is frequently light spotting or bleeding, but it may be moderate or heavy. If you experience vaginal bleeding while taking femhrt 1/5, discuss your bleeding pattern with your healthcare provider.

In addition to the risks and side effects just listed, patients taking estrogen or progestin have reported the following side effects:

- nausea and vomiting
- breast tenderness or enlargement
- headache
- retention of extra fluid (edema), which may make some conditions worse, such as asthma, epilepsy, migraine, heart disease, or kidney disease
- runny nose
- abdominal pain
- enlargement of non-cancerous tumors (fibroids) of the uterus
- spotty darkening of the skin, particularly on the face; reddening of the skin; skin rashes

These are not all the possible side effects of femhrt 1/5. For more information, ask your healthcare provider or pharmacist.

How can I reduce the risks associated with taking femhrt 1/5?

If you take femhrt 1/5, you can reduce your risks by carefully monitoring your treatment.

- **See your healthcare provider regularly.** Talk with your healthcare provider regularly (every 3-6 months) about whether you should continue taking femhrt 1/5.
- **See your healthcare provider right away if you develop vaginal bleeding while taking femhrt 1/5.**

- **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 more frequent breast examinations.
- **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.
- **Be alert for signs of trouble.** If any of the following warning signs (or any other unusual symptoms) happen while you are taking femhrt 1/5, call your doctor right away:
    - pains in the calves or chest, sudden shortness of breath, or coughing blood (possible clots in the legs, heart, or lungs)
    - severe headache or vomiting, dizziness, faintness, or changes in vision or speech, weakness or numbness of an arm or leg (possible clots in the brain or eye)
    - breast lumps (possible breast cancer)
    - yellowing of the skin or whites of the eyes (possible liver problem)
    - pain, swelling, or tenderness in the abdomen (possible gallbladder problem)

Other Information

- Discuss carefully with your doctor or healthcare provider all the possible risks and benefits of estrogen and progestin treatment as they affect you personally.
- If you take calcium supplements as part of your treatment to help prevent osteoporosis, ask your doctor about the amounts recommended. A daily intake of 1500 mg of calcium is often recommended for postmenopausal women. Vitamin D (400 IU daily) may help your body use more of the calcium.
- Taking estrogens with progestins may have unhealthy effects on blood sugar, which might make a diabetic condition worse.
- Your doctor has prescribed this drug for you and you alone. Do not give your femhrt 1/5 to anyone else. Do not take femhrt 1/5 for conditions for which it was not prescribed.
- Keep all drugs out of the reach of children. In case of overdose, call you doctor, hospital, or poison control center right away.

What are the ingredients in femhrt 1/5?

Each white D-shaped tablet contains 1 mg norethindrone acetate [19-Norpregn-4-en-20-yn-3-one, 17-(acetyloxy)-, (17α)-] and 5 mcg ethinyl estradiol [19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)-]. Each tablet also contains calcium stearate, lactose monohydrate, microcrystalline cellulose, and cornstarch.

This leaflet provides the most important information about femhrt 1/5. If you want more information, ask your doctor or pharmacist for the professional labeling. The professional labeling is published in a book called "The Physicians' Desk Reference" or PDR, available in bookstores and public libraries.

Manufactured by:
Duramed Pharmaceuticals, Inc.
Cincinnati, OH 45213

Marketed by:
Warner Chilcott, Inc.
Rockaway, NJ 07866

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