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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-633

Approved Labeling

PRESCRIBING INFORMATION

Femtrace® (estradiol acetate tablets)

Rx Only

ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER

Close clinical surveillance of all women taking estrogens 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 at equivalent estrogen doses. (See **WARNINGS, Malignant neoplasms, Endometrial cancer.**)

CARDIOVASCULAR AND OTHER RISKS

Estrogens with or without progestins should not be used for the prevention of cardiovascular disease. (See **WARNINGS, Cardiovascular disorders.**)

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.**)

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 or to women taking estrogen alone therapy. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)

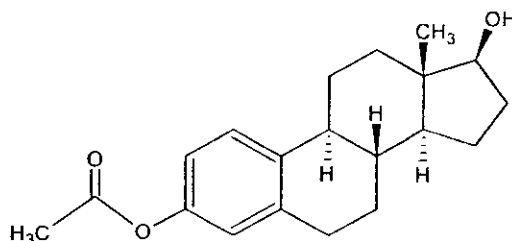
Other doses of oral conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens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

Femtrace® (estradiol acetate tablets) for oral administration contains 0.45 mg, 0.9 mg or 1.8 mg estradiol acetate.

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

Estradiol acetate is chemically described as estra-1,3,5(10)-triene-3,17 β -diol-3-acetate. The molecular formula of estradiol acetate is C₂₀H₂₆O₃ and the structural formula is:



The molecular weight of estradiol acetate is 314.42.

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 estrinol, 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.

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.

Pharmacokinetics

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

Absorption

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

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

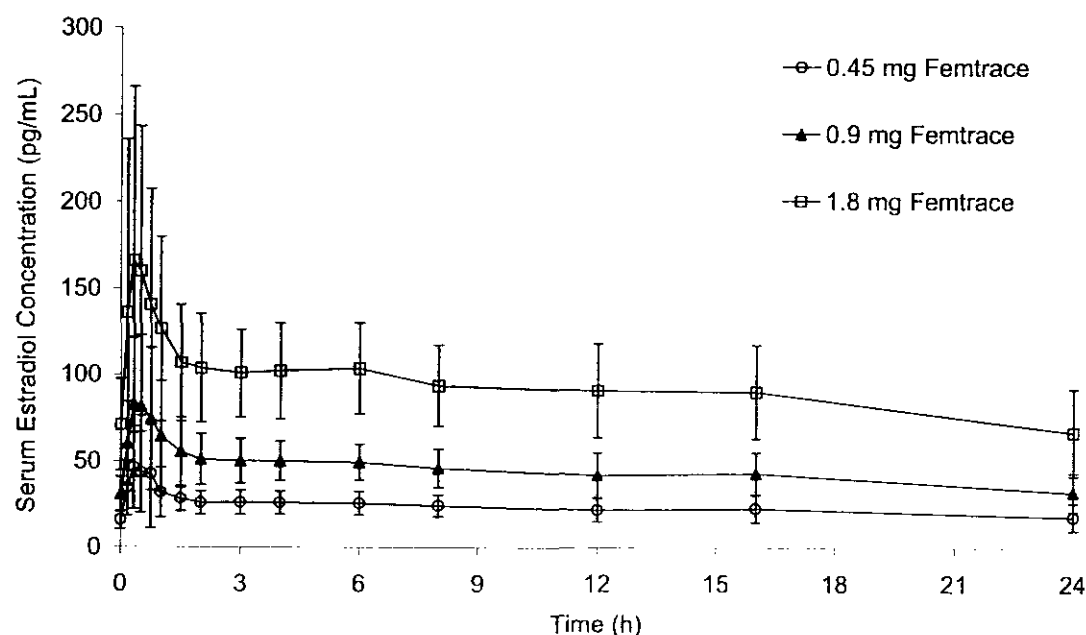


Table 1. Summary of Mean (%CV)* Pharmacokinetic Parameters Following Multiple-Dose Administration of Femtrace to Healthy Postmenopausal Women (n=18)

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

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

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

Effect of Food

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

Distribution

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

Metabolism

Estradiol acetate is hydrolyzed *in vivo* to estradiol. Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is 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.

Excretion

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

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

Special Populations

No pharmacokinetic studies were conducted in special populations, including patients with renal or hepatic impairment.

Drug Interactions

No clinical drug-drug interaction studies with estradiol acetate have been performed. *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.

Two 12-week double-blind, placebo-controlled clinical trials were conducted to evaluate the efficacy of Femtrace in the treatment of moderate to severe vasomotor symptoms in postmenopausal women who had at least 7 moderate to severe hot flushes daily or at least 60 moderate to severe hot flushes per week before randomization. In one study, 289 postmenopausal women (mean age 53.4 years [range 41 to 68 years], 78% Caucasian) were randomized to receive either placebo, Femtrace 0.9 mg/day or Femtrace 1.8 mg/day. In the second study, 221 postmenopausal women (mean age 52.2 years [range 36 to 80 years], 80% Caucasian) were randomized to receive either placebo or Femtrace 0.45 mg/day. The results in Tables 2a and 3a indicate that compared with placebo, Femtrace 0.9 mg/day and Femtrace 1.8 mg/day produced a reduction in both the frequency and severity of moderate to severe vasomotor symptoms at weeks 4 and 12. The results in Tables 2b and 3b indicate that compared with placebo, Femtrace 0.45 mg/day produced a reduction in the frequency of moderate to severe vasomotor symptoms at weeks 4 and 12, and a reduction in the severity of moderate to severe vasomotor symptoms at weeks 7 and 12.

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

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

*Primary endpoints

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

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

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

Table 2b. Mean Change from Baseline in the Number of Moderate to Severe Vasomotor Symptoms per Week – ITT (modified)¹ Population, LOCF

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

*Primary endpoints

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

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

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

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

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

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

*Primary endpoints

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

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

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

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

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

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

*Primary endpoints

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

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

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

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

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

Women's Health Initiative Studies

The Women's Health Initiative (WHI) study 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 4 below.

Table 4. 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>	1.32 (1.02 – 1.72)	23	30
<i>CHD death</i>	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”, 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 WARNINGS, 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

Femtrace therapy is indicated in the treatment of moderate to severe vasomotor symptoms associated with the menopause.

CONTRAINDICATIONS

Femtrace 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 the past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction).
6. Liver dysfunction or disease.
7. Femtrace should not be used in patients with known hypersensitivity to its ingredients.
8. Known or suspected pregnancy. There is no indication for Femtrace 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 WARNINGS.**

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, estrogens 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 myocardial infarctions and strokes has been observed in women receiving CE compared to placebo. These observations are preliminary. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)

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.

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.

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 has been observed in women receiving CE compared to placebo. These observations are preliminary. (See **CLINICAL PHARMACOLOGY, Clinical Studies**.)

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.

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

2. Malignant neoplasms

a. 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.

b. 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 apparently 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.

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.**)

It is unknown whether these findings apply to estrogen alone therapy.

4. Gallbladder disease

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

5. 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

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

There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include 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 a 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 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 Femtrace.

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

1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of antifactor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.
2. Increased thyroid-binding globulin (TBG) levels leading to increased circulating total thyroid hormone levels as measured by protein-bound iodine (PBI), T₄ levels (by column or by radioimmunoassay) or T₃ levels by radioimmunoassay. T₃ resin uptake is decreased, reflecting the elevated TBG. Free T₄ and free T₃ concentrations are unaltered. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.
3. Other binding proteins may be elevated in serum (i.e., corticosteroid binding globulin (CBG), sex hormone binding globulin (SHBG)) leading to increased total 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).
4. Increased plasma HDL and HDL₂ cholesterol subfraction concentrations, reduced LDL cholesterol concentration, increased triglycerides levels.
5. Impaired glucose tolerance.
6. Reduced response to metyrapone test.

E. Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term continuous administration of estrogen, with or without progestin, in women with and without a uterus, has shown an increased risk of endometrial cancer, breast cancer and ovarian cancer. (See **BOXED WARNINGS**, **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. Estradiol acetate was assayed for mutation in four histidine-requiring strains of *Salmonella typhimurium* and in one tryptophan-requiring strains of *Escherichia coli*. Estradiol acetate did not induce mutations in any of the bacterial strains tested under the conditions employed.

F. Pregnancy

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

G. Nursing Mothers

Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving this drug. Caution should be exercised when Femtrace is administered to a nursing woman.

H. Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

I. Geriatric Use

Clinical studies of Femtrace did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greatest frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

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.**)

It is unknown whether these findings apply to estrogen alone therapy.

ADVERSE REACTIONS

See **BOXED WARNINGS, 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.

In two 12-week clinical trials that included 327 postmenopausal women treated with Femtrace and 221 women treated with placebo tablets, adverse events that occurred in any treatment group at a rate of $\geq 2\%$ regardless of drug relationship are summarized in Table 5.

Table 5. Incidence of AEs Occurring in $\geq 2\%$ of Subjects in Any Treatment Group Presented in Descending Frequency of Preferred Term

Adverse Event ^a	Placebo	Femtrace	Femtrace	Femtrace
	(n = 221)	0.45 mg/day (n = 132)	0.9 mg/day (n = 100)	1.8 mg/day (n = 95)
	n (%)	n (%)	n (%)	n (%)
Headache (NOS)	12 (5.4)	4 (3.0)	5 (5.0)	4 (4.2)
Vaginal Bleeding	3 (1.4)	1 (0.8)	4 (4.0)	7 (7.4)
Breast Tenderness	3 (1.4)	1 (0.8)	0 (0.0)	6 (6.3)
Influenza	3 (1.4)	3 (2.3)	0 (0.0)	4 (4.2)
Vaginal Discharge	0 (0.0)	3 (2.3)	4 (4.0)	3 (3.2)
Abdominal Pain (NOS)	4 (1.8)	1 (0.8)	0 (0.0)	3 (3.2)
Fungal Infection (NOS)	2 (0.9)	4 (3.0)	1 (1.0)	1 (1.1)
Nasopharyngitis	5 (2.3)	2 (1.5)	0 (0.0)	1 (1.1)
Nausea	3 (1.4)	3 (2.3)	0 (0.0)	2 (2.1)
Intermenstrual Bleeding	2 (0.9)	0 (0.0)	2 (2.0)	3 (3.2)
Sinusitis (NOS)	3 (1.4)	2 (1.5)	1 (1.0)	1 (1.1)
Upper Respiratory Tract Infection (NOS)	3 (1.4)	1 (0.8)	3 (3.0)	0 (0.0)
Back Pain	1 (0.5)	0 (0.0)	3 (3.0)	2 (2.1)
Bronchitis (NOS)	1 (0.5)	2 (1.5)	2 (2.0)	1 (1.1)

AE = adverse event; NOS = not otherwise specified

^a Regardless of drug relationship

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; dysmenorrhea; 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

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

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

5. Skin

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

6. Eyes

Retinal vascular thrombosis; intolerance to contact lenses.

7. Central nervous system

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 estrogen-containing drug products by young children. Overdosage of estrogen may cause nausea and vomiting, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION

When estrogen is prescribed for a postmenopausal woman with a uterus, a progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin. Use of estrogen, alone or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be reevaluated periodically as clinically appropriate (e.g., 3-month to 6-month intervals) to determine if treatment is still necessary (see **BOXED WARNINGS** 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.

Femtrace therapy consists of a single tablet to be taken once daily.

Three doses of Femtrace are available, 0.45 mg/day, 0.9 mg/day and 1.8 mg/day, for the treatment of moderate to severe vasomotor symptoms associated with the menopause.

Patients should be started at the lowest dose.

HOW SUPPLIED

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

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

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

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

Keep out of reach of children.

STORAGE

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

Manufactured by: Pharmaceuticals International, Inc., Hunt Valley, MD 21301
Marketed by: Warner Chilcott Inc., Rockaway, NJ 07866



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REVISED August 2004

PATIENT INFORMATION

(Updated August 20, 2004)

Femtrace[®] (estradiol acetate tablets)

Read this PATIENT INFORMATION before you start taking Femtrace and read what you get each time you refill Femtrace. 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 FEMTRACE (AN ESTROGEN HORMONE)?

- Estrogens increase the chances of getting cancer of the uterus.

Report any unusual vaginal bleeding right away while you are taking estrogens. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.

- Do not use estrogens with or without progestins to prevent heart disease, heart attacks or strokes.

Using estrogens with or without progestins may increase your chances of getting heart attacks, strokes, breast cancer and blood clots. Using estrogens with progestins may increase your risk of dementia. You and your healthcare provider should talk regularly about whether you still need treatment with Femtrace.

What is Femtrace?

Femtrace is a medicine that contains an estrogen hormone.

What is Femtrace used for?

Femtrace is used after menopause to:

- **reduce moderate to severe hot flashes.**
Estrogens are hormones made by a woman's ovaries. The ovaries normally stop making estrogens when a woman is between 45 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 the estrogen levels begin dropping, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden strong feelings of heat and sweating ("hot flashes" or "hot flushes"). In some women the symptoms are mild and they will not need estrogens. In other women, symptoms can be more severe. You and your healthcare provider should talk regularly about whether you still need treatment with Femtrace.

Who should not use Femtrace?

Do not start taking Femtrace if you:

- **have unusual vaginal bleeding**
- **currently have or have had certain cancers**
Estrogens may increase the chances of getting certain types of cancers, including cancer of the breast or uterus. If you have or had cancer, talk with your healthcare provider about whether you should take Femtrace.
- **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 Femtrace or any of its ingredients**
See the end of this leaflet for a list of ingredients in Femtrace.
- **think you may be pregnant**

Tell your healthcare provider:

- **if you are breastfeeding**
The hormone in Femtrace 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**
This includes prescription and nonprescription medicines, vitamins and herbal supplements. Some medicines may affect how Femtrace works. Femtrace 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.

How should I take Femtrace?

1. Take one Femtrace tablet daily.
2. Start at the lowest dose and talk to your healthcare provider about how well that dose is working for you.

3. Estrogens should be used at the lowest dose possible for your treatment only as long as needed. You and your healthcare provider should talk regularly (for example, every 3 to 6 months) about the dose you are taking and whether you still need treatment with Femtrace.

What are the possible side effects of estrogens?

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 Femtrace. For more information, ask your healthcare provider or pharmacist.

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

- Talk with your healthcare provider regularly about whether you should continue taking Femtrace.
- If you have a uterus, talk to your healthcare provider about whether the addition of a progestin is right for you.
- See your healthcare provider right away if you get vaginal bleeding while taking Femtrace.
- 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, 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 if you use tobacco, you may have higher chances of getting heart disease. Ask your healthcare provider for ways to lower your chances for getting heart disease.

General information about safe and effective use of Femtrace.

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

Keep Femtrace out of the reach of children.

This leaflet provides a summary of the most important information about Femtrace. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about Femtrace that is written for health professionals. You can also get more information by calling the toll free number 800-521-8813.

What are the ingredients in Femtrace?

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

Rx Only

Manufactured by: Pharmaceuticals International, Inc., Hunt Valley, MD 21301
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78 Page(s) Withheld

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