PRESCRIBING INFORMATION

Femring®
(estradiol acetate vaginal ring)
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 or dementia. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular disorders** and **Dementia**.)

The estrogen-alone substudy of the Women's Health Initiative (WHI) reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 6.8 years and 7.1 years, respectively, of treatment with oral conjugated estrogens (CE 0.625 mg) per day relative to placebo. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular disorders**.)

The estrogen-plus-progestin substudy of WHI 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 5.6 years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) per day, relative to placebo. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular disorders** and **Malignant neoplasms, *Breast cancer*.**)

The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with CE 0.625 mg alone and during 4 years of treatment with CE 0.625 mg combined with MPA 2.5 mg, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See **CLINICAL STUDIES** and **WARNINGS, Dementia** and **PRECAUTIONS, Geriatric Use**.)

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

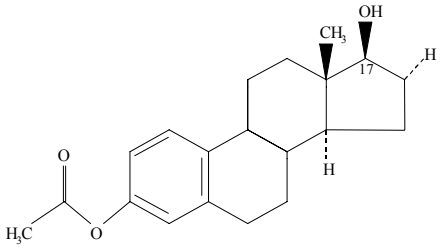
DESCRIPTION

Femring® (estradiol acetate vaginal ring) is an off-white, soft, flexible ring with a central core containing estradiol acetate.

Femring is made of cured silicone elastomer composed of dimethyl polysiloxane silanol, silica (diatomaceous earth), normal propyl orthosilicate, stannous octoate; barium sulfate and estradiol acetate. The rings have the following dimensions: outer diameter 56 mm, cross-sectional diameter 7.6 mm, core diameter 2 mm.

Femring is available in two strengths: Femring 0.05 mg/day has a central core that contains 12.4 mg of estradiol acetate, which releases at a rate equivalent to 0.05 mg of estradiol per day for 3 months. Femring 0.10 mg/day has a central core that contains 24.8 mg of estradiol acetate, which releases at a rate equivalent to 0.10 mg of estradiol per day for 3 months.

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



The molecular weight of estradiol acetate is 314.41.

CLINICAL PHARMACOLOGY

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

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

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.

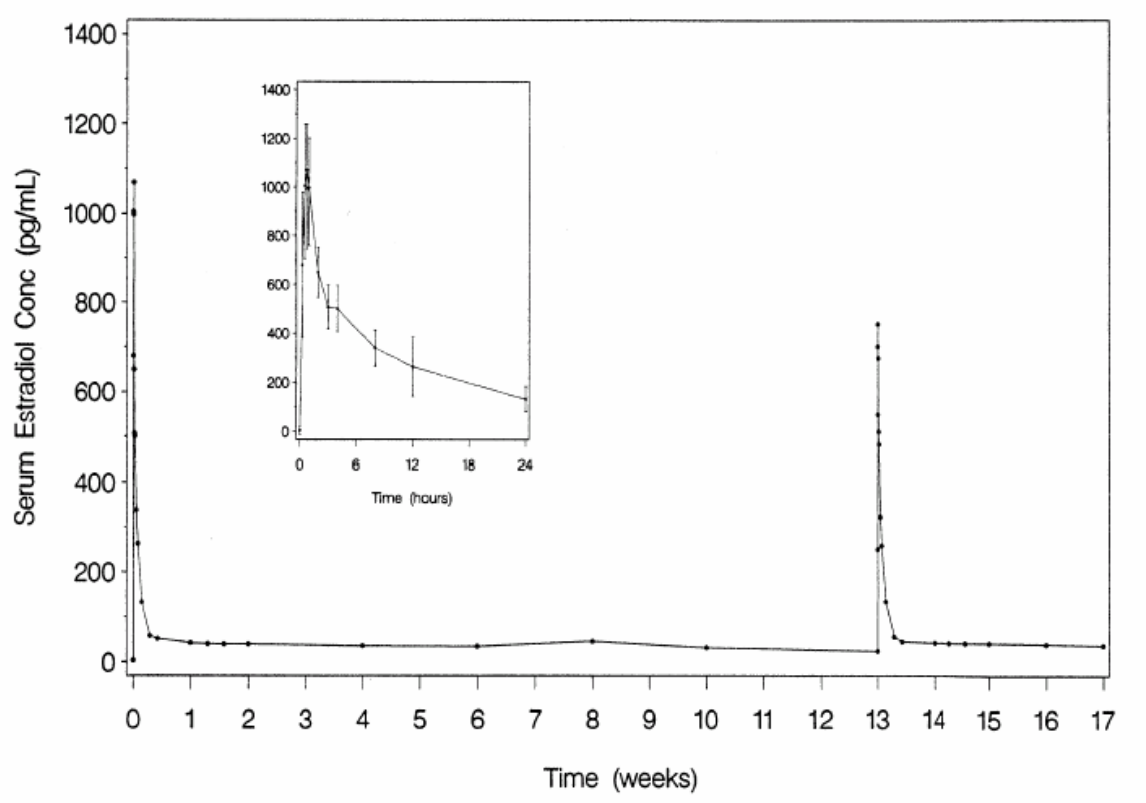
Pharmacokinetics

Estradiol acetate is rapidly hydrolyzed to estradiol.

A. Absorption

Drug delivery from Femring is rapid for the first hour and then declines to a relatively constant rate for the remainder of the 3-month dosing interval. In vitro studies have shown that this initial release is higher as the rings age upon storage. Estradiol acetate and estradiol are rapidly absorbed through the vaginal mucosa as evidenced by t_{max} values for estradiol of less than 1 hour. Following C_{max}, serum estradiol concentrations decrease rapidly such that by 24 to 48 hours postdose, serum estradiol concentrations are relatively constant through the end of the 3-month dosing interval, see **Figure 1** for results from rings stored for 16 months.

Figure 1. Mean serum estradiol concentrations following multiple dose administration of Femring (0.05 mg/day estradiol) (second dose administered at 13 weeks) (inset: mean (±SD) of serum concentration-time profile for dose 1 from 0-24 hours)



Following administration of Femring (0.05 mg/day estradiol), average serum estradiol concentration was 40.6 pg/mL; the corresponding apparent in vivo estradiol delivery rate was

0.052 mg/day. Following administration of Femring (0.10 mg/day estradiol), average serum estradiol concentration was 76 pg/mL; apparent in vivo delivery rate was 0.097 mg/day. Results are summarized in **Table 1** below.

Table 1. Summary of Mean (%RSD)* Pharmacokinetic Parameters for Femring

Dose (as estradiol)		Number of subjects	Cmax (pg/mL)	Tmax (hour)	Cavg (pg/mL)
0.05 mg/day	Estradiol[1]	25	1129 (25)	0.9 (41)	40.6 (26)
	Estrone[1]	25	141 (25)	6.2 (84)	35.9 (21)
	Estrone sulfate[1]	25	2365 (44)	9.3 (39)	494.6 (48)
0.10 mg/day	Estradiol[2]	12	1665 (23)	0.7 (90)	--[4]
	Estradiol[3]	11	--	--	76.0 (24)
	Estrone[3]	11	--	--	45.7 (25)

* Relative Standard Deviation, [1]Study 1, [2]Study 2, [3]Study 3, [4]-- Not determined

Consistent with the avoidance of first pass metabolism achieved by vaginal estradiol administration, serum estradiol concentrations were slightly higher than estrone concentrations.

B. 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.

C. Metabolism

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

D. Excretion

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

E. Special Populations

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

F. Drug Interactions

In vitro and in vivo studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations (Hypericum perforatum),

phenobarbital, carbamazepine and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

CLINICAL STUDIES

Effects on vasomotor symptoms.

A 13-week double-blind, placebo-controlled clinical trial was conducted to evaluate the efficacy of 2 doses of the vaginal ring in the treatment of moderate to severe vasomotor symptoms in 333 postmenopausal women between 29 and 85 years of age (mean age 51.7 years, 77% were Caucasian) who had at least 7 moderate to severe hot flushes daily or at least 56 moderate to severe hot flushes per week before randomization. Patients were randomized to receive either placebo, Femring 0.05 mg/day or Femring 0.10 mg/day. Femring 0.05 mg/day and Femring 0.10 mg/day were shown to be statistically better than placebo at weeks 4 and 12 for relief of both the frequency and severity of moderate to severe vasomotor symptoms. Frequency results are shown in **Table 2**. Severity results are shown in **Table 3**.

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

Visit	Placebo (n = 105)	Estradiol 0.05 mg/day (n = 111)	Estradiol 0.10 mg/day (n = 109)
Baseline [1]			
Mean (SD)	83.62 (60.42)	73.83 (24.53)	75.11 (25.44)
Week 4			
Mean (SD)	51.14 (51.19)	21.59* (27.76)	11.37* (19.43)
Mean Change from Baseline (SD)	-32.48 (46.25)	-52.24* (32.92)	-63.75* (26.68)
p value vs. Placebo (95% CI) [2]	-	<0.001 (-30.7, -8.8)	<0.001 (-42.2, -20.3)
Week 12			
Mean (SD)	42.21 (41.13)	15.48* (25.42)	8.25* (16.58)
Mean Change from Baseline (SD)	-41.41 (65.61)	-58.36* (31.36)	-66.87* (27.44)
p value vs. Placebo (95% CI) [2]	-	0.006 (-30.5, -3.4)	<0.001 (-39.1, -11.8)

*Denotes statistical significance at the 0.050 level

[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 and confidence intervals are from a two-way ANOVA with factors for treatment and study center for the difference between treatment groups in the mean change from baseline. Confidence intervals are adjusted for multiple comparisons within each timepoint using Dunnett's method.

ITT = intent to treat; LOCF = last observation carried forward; CI = confidence interval

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

Visit	Placebo (n = 105)	Estradiol 0.05 mg/day (n = 111)	Estradiol 0.10 mg/day (n = 109)
Baseline [1]			
Mean (SD)	2.51 (0.26)	2.46 (0.23)	2.48 (0.24)
Week 4			
Mean (SD)	2.23 (0.71)	1.67* (1.07)	1.15* (1.14)
Mean Change from Baseline (SD)	-0.28 (0.69)	- 0.79* (1.08)	-1.33* (1.10)
p value vs. Placebo (95% CI) [2]	-	<0.001 (-0.8, -0.2)	<0.001 (-1.3, -0.8)
Week 12			
Mean (SD)	2.00 (0.96)	1.41* (1.17)	0.92* (1.09)
Mean Change from Baseline (SD)	-0.51 (0.94)	-1.06* (1.16)	-1.56* (1.06)
p value vs. Placebo (95% CI) [2]	-	<0.001 (-0.9, -0.2)	<0.001 (-1.4, -0.7)

*Denotes statistical significance at the 0.050 level

[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 and confidence intervals are from a two-way ANOVA with factors for treatment and study center for the difference between treatment groups in the mean change from baseline. Confidence intervals are adjusted for multiple comparisons within each timepoint using Dunnett's method.

ITT = intent to treat; LOCF = last observation carried forward; CI = confidence interval

Effects on vulvar and vaginal atrophy.

In the same 13-week clinical trial, vaginal superficial cells increased by a mean of 16.0% and 18.9% for Femring 0.05 mg/day and Femring 0.10 mg/day, respectively, as compared to 1.11% for placebo at week 13. A corresponding reduction in parabasal cells was observed at week 13. Vaginal pH decreased for Femring 0.05 mg/day and Femring 0.10 mg/day by a mean of 0.73 and 0.60, respectively, compared to a mean decrease of 0.25 in the placebo group.

Women's Health Initiative Studies

The Women's Health Initiative (WHI) study enrolled a total of 27,000 predominantly healthy postmenopausal women in two substudies 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 (MI), silent MI 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 (only in CE/MPA), 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 estrogen-alone substudy was stopped early because an increased risk of stroke was observed, and it was deemed that no further information would be obtained regarding the risks and benefits of estrogen alone in predetermined primary endpoints. Results of the estrogen-alone substudy, which included 10,739 women (average age of 63 years, range 50 to 79; 75.3% White, 15.1% Black, 6.1% Hispanic, 3.6% Other) after an average follow-up of 6.8 years, are presented in **Table 4** below.

TABLE 4. RELATIVE AND ABSOLUTE RISK SEEN IN THE ESTROGEN-ALONE SUBSTUDY OF WHI

Event	Relative Risk CE vs. Placebo (95% nCI[a])	CE n = 5,310	Placebo n = 5,429
		Absolute Risk per 10,000 Women-Years	
CHD events[b]	0.95 (0.79-1.16)	53	56
Non-fatal MI[b]	*0.91 (0.73-1.14)*	*40*	*43*
CHD death[b]	*1.01 (0.71-1.43)*	*16*	*16*
Stroke[c]	1.39 (1.10-1.77)	44	32
Deep vein thrombosis[b,d]	1.47 (1.06-2.06)	23	15
Pulmonary embolism[b]	1.37 (0.90-2.07)	14	10
Invasive breast cancer[b]	0.80 (0.62-1.04)	28	34
Colorectal cancer[c]	1.08 (0.75-1.55)	17	16
Hip fracture[c]	0.61 (0.41-0.91)	11	17
Vertebral fractures[c,d]	0.62 (0.42-0.93)	11	17
Total fractures[c,d]	0.70 (0.63-0.79)	139	195
Death due to other causes[c,e]	1.08 (0.88-1.32)	53	50
Overall mortality[c,d]	1.04 (0.88–1.22)	81	78
Global Index[c,f]	1.01 (0.91-1.12)	192	190

[a]Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.

[b]Results are based on centrally adjudicated data for an average follow-up of 7.1 years.

[c]Results are based on an average follow-up of 6.8 years.

[d]Not included in Global Index.

[e]All deaths, except from breast or colorectal cancer, definite/probable CHD, PE or cerebrovascular disease.

[f]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, colorectal cancer, hip fracture, or death due to other causes.

For those outcomes included in the WHI "global index" that reached statistical significance, the absolute excess risk per 10,000 women-years in the group treated with CE alone were 12 more strokes while the absolute risk reduction per 10,000 women-years was six fewer hip fractures. The absolute excess risk of events included in the "global index" was a nonsignificant two events per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality. (See **BOXED WARNINGS**, **WARNINGS**, and **PRECAUTIONS**.)

Final adjudicated results for CHD events from the estrogen-alone substudy, after an average follow-up of 7.1 years, reported no overall difference for primary CHD events (nonfatal MI, silent MI and CHD death) in women receiving CE alone compared with placebo (see **Table 4**).

The CE/MPA substudy was also stopped early. According to the predefined stopping rule, after an average follow-up of 5.2 years of treatment, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the "global index". The absolute excess risk of events included in the "global index" was 19 per 10,000 women-years (RR 1.15, 95% nCI 1.03-1.28).

For those outcomes included in the WHI "global index" that reached statistical significance after 5.6 years of follow-up, the absolute excess risks per 10,000 women-years in the group treated with CE/MPA were six more CHD events, seven more strokes, ten more PEs, and eight more invasive breast cancers, while the absolute risk reductions per 10,000 women-years were seven fewer colorectal cancers and five fewer hip fractures. (See **BOXED WARNINGS**, **WARNINGS**, and **PRECAUTIONS**.)

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, 3.9% Other), after an average follow-up of 5.6 years are presented in **Table 5** below.

TABLE 5. RELATIVE AND ABSOLUTE RISK SEEN IN THE ESTROGEN-PLUS-PROGESTIN SUBSTUDY OF WHI AT AN AVERAGE OF 5.6 YEARS[a]

Event	Relative Risk CE/MPA vs. Placebo (95% nCI[b])	CE/MPA n = 8,506	Placebo n = 8,102
		Absolute Risk per 10,000 Women-Years	
CHD events	1.24 (1.00-1.54)	39	33
Non-fatal MI	*1.28 (1.00-1.63)*	*31*	*25*
CHD death	*1.10 (0.70-1.75)*	*8*	*8*
All strokes	1.31 (1.02-1.68)	31	24
Ischemic Stroke	*1.44 (1.09-1.90)*	*26*	*18*
Deep vein thrombosis	1.95 (1.43-2.67)	26	13

Pulmonary embolism	2.13 (1.45-3.11)	18	8
Invasive breast cancer[c]	1.24 (1.01-1.54)	41	33
Invasive colorectal cancer	0.56 (0.38-0.81)	9	16
Endometrial cancer	0.81 (0.48-1.36)	6	7
Cervical cancer	1.44 (0.47-4.42)	2	1
Hip fracture	0.67 (0.47-0.96)	11	16
Vertebral fractures	0.65 (0.46-0.92)	11	17
Lower arm/wrist fractures	0.71 (0.59-0.85)	44	62
Total fractures	0.76 (0.69-0.83)	152	199

[a]Results are based on centrally adjudicated data. Mortality data was not part of the adjudicated data; however, data at 5.2 years of follow-up showed no difference between the groups in terms of all-cause mortality (RR 0.98, 95% nCI 0.82-1.18).

[b]Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.

[c]Includes metastatic and non-metastatic breast cancer, with the exception of in situ breast cancer.

Women's Health Initiative Memory Study

The estrogen-alone Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, enrolled 2,947 predominantly healthy postmenopausal women 65 years of age and older (45%, age 65 to 69 years; 36%, 70 to 74 years; 19%, 75 years of age and older) to evaluate the effects of CE 0.625 mg daily on the incidence of probable dementia (primary outcome) compared with placebo.

After an average follow-up of 5.2 years, 28 women in the estrogen-alone group (37 per 10,000 women-years) and 19 in the placebo group (25 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the estrogen-alone group was 1.49 (95% CI 0.83–2.66) compared to placebo. It is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNINGS**, **WARNINGS, Dementia** and **PRECAUTIONS, Geriatric Use**.)

The estrogen-plus-progestin WHIMS substudy 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.

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95% CI 1.19-2.60). Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNINGS**, **WARNINGS**, **Dementia** and **PRECAUTIONS**, **Geriatric Use**.)

INDICATIONS AND USAGE

Femring therapy is indicated in the:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.
2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.

CONTRAINDICATIONS

Femring 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. Femring should not be used in patients with known hypersensitivity to its ingredients.
8. Known or suspected pregnancy. There is no indication for Femring 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-alone therapy has been associated with an increased risk of stroke and deep vein thrombosis (DVT).

Estrogen-plus-progestin therapy has been associated with an increased risk of myocardial infarction as well as stroke, venous thrombosis and pulmonary embolism.

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. Stroke

In the estrogen-alone substudy of the Women's Health Initiative (WHI) study, a statistically significant increased risk of stroke was reported in women receiving CE 0.625 mg daily compared to women receiving placebo (44 vs. 32 per 10,000 women-years). The increase in risk was demonstrated in year one and persisted. (See **CLINICAL STUDIES**.)

In the estrogen-plus-progestin substudy of WHI, a statistically significant increased risk of stroke was reported in women receiving CE/MPA 0.625 mg/2.5 mg daily compared to women receiving placebo (31 vs. 24 per 10,000 women-years). The increase in risk was demonstrated after the first year and persisted.

b. Coronary heart disease

In the estrogen-alone substudy of WHI, no overall effect on coronary heart disease (CHD) events (defined as non-fatal MI, silent MI, or death, due to CHD) was reported in women receiving estrogen alone compared to placebo. (See **CLINICAL STUDIES**.)

In the estrogen-plus-progestin substudy of WHI, no statistically significant increase of CHD events was reported in women receiving CE/MPA compared to women receiving placebo (39 vs. 33 per 10,000 women years). An increase in relative risk was demonstrated in year one, and a trend toward decreasing relative risk was reported in years 2 through 5.

In postmenopausal women with documented heart disease (n = 2,763, average age 66.7 years) a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study; HERS) treatment with CE/MPA 0.625 mg conjugated estrogens/2.5 mg medroxyprogesterone acetate daily 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 one, 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 the HERS, the 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.

c. Venous thromboembolism (VTE)

In the estrogen-alone substudy of WHI, the risk of VTE (DVT and pulmonary embolism [PE]), was reported to be increased for women taking conjugated estrogens (30 vs. 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 vs. 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first two years. (See **CLINICAL STUDIES**.)

In the estrogen-plus-progestin substudy of WHI, a statistically significant 2-fold greater rate of VTE was reported in women receiving CE/MPA compared to women receiving placebo (35 vs. 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 vs. 13 per 10,000 women-years) and PE (18 vs. 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was demonstrated 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 nonusers, 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

In some studies, 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 STUDIES**). The results from observational studies are generally consistent with those of the WHI clinical trial.

Observational studies have also reported an increased risk for estrogen-plus-progestin combination therapy and a smaller increased risk for estrogen alone therapy after several years of use. For both findings, the excess risk increased with duration of use, and appeared to return to baseline over about five years after stopping treatment (only the observational studies have substantial data on risk after stopping). In these studies, the risk of breast cancer was greater, and became apparent earlier, with estrogen-plus-progestin combination therapy as compared to estrogen-alone therapy. However, these studies have not found significant variation in the risk of breast cancer among different estrogens or among different estrogen-plus-progestin combinations, doses, or routes of administration.

In the estrogen-alone substudy of WHI, after an average of 7.1 years of follow-up, CE (0.625 mg daily) was not associated with an increased risk of invasive breast cancer (RR 0.80, 95 % nCI 0.62-1.04).

In the estrogen-plus-progestin substudy, after a mean follow-up of 5.6 years, the WHI substudy reported an increased risk of breast cancer. In this substudy, prior use of estrogen alone or estrogen-plus-progestin combination hormone therapy was reported by 26% of the women. The relative risk of invasive breast cancer was 1.24 (95% nCI 1.01-1.54), and the 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 WHI trial, 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 alone and estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors and prior mammogram results.

3. Dementia

In the estrogen-alone Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, a population of 2,947 hysterectomized women aged 65 to 79 years was randomized to CE (0.625 mg daily) or placebo. In the estrogen-plus-progestin WHIMS substudy, a population of 4,532 postmenopausal women aged 65 to 79 years was randomized to CE/MPA (0.625 mg/2.5 mg daily) or placebo.

In the estrogen-alone substudy, after an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE alone vs. placebo was 1.49 (95% CI 0.83-2.66). The absolute risk of probable dementia for CE alone vs. placebo was 37 vs. 25 cases per 10,000 women-years.

In the estrogen-plus-progestin substudy, after an average follow-up of four years, 40 women in the estrogen-plus-progestin group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for estrogen plus progestin vs. placebo was 2.05 (95% CI 1.21-3.48). The absolute risk of probable dementia for CE/MPA vs. placebo was 45 vs. 22 cases per 10,000 women-years.

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95% CI 1.19-2.60).Since both substudies were conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNINGS** and **PRECAUTIONS, Geriatric Use**.)

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, adverse effects on lipoprotein metabolism (e.g., lowering HDL, raising LDL) and impairment of glucose tolerance.

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 preexisting 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 T_4 and T_3 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 after an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE/MPA versus placebo was 1.58 (95% nCI 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.

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.

11. Vaginal use and expulsion

Femring may not be suitable for women with conditions that make the vagina more susceptible to vaginal irritation or ulceration, or make expulsions more likely, such as narrow vagina, vaginal stenosis, vaginal infection, cervical prolapse, rectoceles and cystoceles. If local treatment of a vaginal infection is required, Femring can remain in place during treatment.

12. Toxic Shock Syndrome (TSS)

A few cases of toxic shock syndrome (TSS) have been reported in women using vaginal rings. TSS is a rare, but serious disease that may cause death. Warning signs of TSS include fever, nausea, vomiting, diarrhea, muscle pain, dizziness, faintness, or a sunburn-rash on face and body.

B. Patient Information

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

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 and without progestin, in women with and without a uterus, has shown an increased risk of endometrial cancer, breast cancer and ovarian cancer. (See **BOXED 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 two tryptophan-requiring strains of *Escherichia coli.* Estradiol acetate did not induce mutation in any of the bacterial strains tested under the conditions employed.

F. Pregnancy

Femring 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 Femring 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 Femring 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.

Of the total number of subjects in the estrogen-alone substudy of the Women's Health Initiative (WHI) study, 46% (n=4,943) were 65 years and over, while 7.1% (n=767) were 75 years and over. There was a higher relative risk (CE vs. placebo) of stroke in women less than 75 years of age compared to women 75 years and over.

In the estrogen-alone Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, a population of 2,947 hysterectomized women, aged 65 to 79 years, was randomized to CE (0.625 mg daily) or placebo. After an average follow-up of 5.2 years, the relative risk (CE vs. placebo) of probable dementia was 1.49 (95% CI 0.83-2.66). The absolute risk of developing

probable dementia with estrogen alone was 37 vs. 25 cases per 10,000 women-years with placebo.

Of the total number of subjects in the estrogen-plus-progestin substudy of the Women's Health Initiative study, 44% (n=7,320) were 65–74 years of age, while 6.6% (n=1,095) were 75 years and over. There was a higher relative risk (CE/MPA vs. placebo) of non-fatal stroke and invasive breast cancer in women 75 and over compared to women less than 75 years of age. In women greater than 75, the increased risk of non-fatal stroke and invasive breast cancer observed in the estrogen-plus-progestin combination group compared to the placebo group was 75 vs. 24 per 10,000 women-years and 52 vs. 12 per 10,000 women-years, respectively.

In the estrogen-plus-progestin WHIMS substudy, a population of 4,532 postmenopausal women, aged 65 to 79 years, was randomized to CE/MPA (0.625 mg/2.5 mg daily) or placebo. In the estrogen-plus-progestin group, after an average follow-up of four years, the relative risk (CE/MPA vs. placebo) of probable dementia was 2.05 (95% CI 1.21-3.48).The absolute risk of developing probable dementia with CE/MPA was 45 vs. 22 cases per 10,000 women-years with placebo.

Seventy-nine percent of the cases of probable dementia occurred in women that were older than 70 for the CE group, and 82 percent of the cases of probable dementia occurred in women who were older than 70 in the CE/MPA group. The most common classification of probable dementia in both the treatment groups and placebo groups was Alzheimer's disease.

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95% CI 1.19-2.60). Since both substudies were conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNINGS** and **WARNINGS, Dementia**.)

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 a 13-week clinical trial that included 225 postmenopausal women treated with Femring and 108 women treated with placebo vaginal rings, adverse events that occurred at a rate of ≥2% are summarized in **Table 6**.

Table 6. Incidence of AEs Occurring in ≥ 2% of Subjects Presented in Descending Frequency of Preferred Term

Adverse Event	Placebo (n = 108)	Estradiol 0.05 mg/day (n = 113)	Estradiol 0.10 mg/day (n = 112)
	n (%)	n (%)	n (%)
Headache (NOS)	10 (9.3)	8 (7.1)	11 (9.8)
Intermenstrual Bleeding	2 (1.9)	9 (8.0)	11 (9.8)
Vaginal Candidiasis	3 (2.8)	7 (6.2)	12 (10.7)
Breast Tenderness	2 (1.9)	7 (6.2)	12 (10.7)
Back Pain	4 (3.7)	7 (6.2)	4 (3.6)
Genital Disorder Female (NOS)	9 (8.3)	3 (2.7)	3 (2.7)
Upper Respiratory Tract Infection (NOS)	6 (5.6)	5 (4.4)	4 (3.6)
Abdominal Distension	3 (2.8)	8 (7.1)	3 (2.7)
Vaginal discharge	9 (8.3)	2 (1.8)	3 (2.7)
Vulvovaginitis (NOS)	7 (6.5)	6 (5.3)	1 (0.9)
Nausea	5 (4.6)	3 (2.7)	2 (1.8)
Arthralgia	4 (3.7)	2 (1.8)	2 (1.8)
Sinusitis (NOS)	2 (1.9)	2 (1.8)	4 (3.6)
Uterine Pain	1 (0.9)	2 (1.8)	5 (4.5)
Nasopharyngitis	3 (2.8)	2 (1.8)	2 (1.8)
Pain in Limb	3 (2.8)	1 (0.9)	3 (2.7)
Urinary Tract Infection (NOS)	2 (1.9)	1 (0.9)	4 (3.6)
Vaginal Irritation	4 (3.7)	1 (0.9)	2 (1.8)

AE = adverse event; NOS = not otherwise specified

The following additional adverse reactions have been reported with estrogens 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; 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
Nausea, vomiting, abdominal cramps, bloating; cholestatic jaundice; increased incidence of gallbladder disease; pancreatitis; enlargement of hepatic hemangiomas.

5. Skin
Chloasma or melasma which 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
Headache, migraine; dizziness; mental depression; chorea; nervousness; mood disturbances; irritability; exacerbation of epilepsy; dementia.

8. Miscellaneous
Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; 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.

Two doses of Femring are available, 0.05 mg/day and 0.10 mg/day, for the treatment of moderate to severe vasomotor symptoms and/or moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause.

Patients should be started at the lowest dose. The lowest effective dose of Femring has not been determined.

Instructions for Use

Hands should be thoroughly washed before and after ring insertion.

Femring Insertion

Insert upon removal from the protective pouch.

The opposite sides of the vaginal ring should be pressed together and inserted into the vagina. The exact position is not critical to its function. When Femring is in place, the patient should not feel anything. If the patient feels discomfort, the vaginal ring is probably not far enough inside the vagina. Gently push Femring further into the vagina.

Femring Use

Femring should remain in place for 3 months and then be replaced by a new Femring.

The patient should not feel Femring when it is in place and it should not interfere with sexual intercourse. Straining upon bowel movement may make Femring move down in the lower part of the vagina. If so, it may be repositioned with a finger.

If Femring is expelled totally from the vagina, it should be rinsed in lukewarm water and reinserted by the patient (or healthcare provider if necessary).

Femring Removal

Femring may be removed by looping a finger through the ring and pulling it out.

For patient instructions, see **PATIENT INFORMATION**.

HOW SUPPLIED

Each Femring® (estradiol acetate vaginal ring) is individually packaged in a pouch consisting of one side medical grade paper and the other side polyester/polyethylene laminate.

NDC 0430-6201-40 Femring® 0.05 mg/day (estradiol acetate vaginal ring) is available in single units.
NDC 0430-6202-40 Femring® 0.10 mg/day (estradiol acetate vaginal ring) is available in single units.

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: Warner Chilcott UK Ltd., Larne, Northern Ireland, UK
Marketed by: Warner Chilcott (US), Inc., Rockaway, NJ 07866

6201G014

REVISED February 2007

PATIENT INFORMATION

(Updated February 2007)

Femring® (estradiol acetate vaginal ring)

Read this PATIENT INFORMATION before you start using Femring® and read what you get each time you refill your Femring prescription. 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 FEMRING (AN ESTROGEN PRODUCT)?

- 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, strokes or dementia.

  Using estrogens with or without progestins may increase your chances of getting heart attacks, strokes, breast cancer and blood clots. Using estrogens with or without progestins may increase your risk of dementia, based on a study of women age 65 years or older. You and your healthcare provider should talk regularly about whether you still need treatment with Femring.

What is Femring?

Femring (estradiol acetate vaginal ring) is an off-white, soft, flexible vaginal ring with a center that contains an estrogen. Femring should be removed after 90 days of continuous use. If continuation of therapy is indicated, a new flexible ring should be replaced

What is Femring used for?

Femring 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 Femring.

- **treat moderate to severe dryness, itching and burning in and around the vagina** You and your healthcare provider should talk regularly about whether you still need treatment with Femring to control these problems. If you use Femring only to treat your dryness, itching and burning in and around your vagina, talk with your healthcare provider about whether a topical vaginal product would be better for you.

Who should not use Femring?

Do not start using Femring 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 use Femring.
- **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 Femring or any of its ingredients.** See the end of this leaflet for a list of ingredients in Femring.
- **think you may be pregnant**

Tell your healthcare provider:

- **if you are breastfeeding.** The hormone in Femring 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 Femring works. Femring 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.

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

- 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

What are the possible side effects of vaginal rings?

A few cases of toxic shock syndrome (TSS) have been reported in women using vaginal rings.

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

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

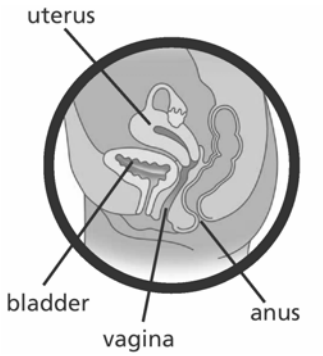
- Talk with your healthcare provider regularly about whether you should continue using Femring.
- See your healthcare provider right away if you get vaginal bleeding while using Femring.
- If you have fever, nausea, vomiting, diarrhea, muscle pain, dizziness, faintness, or a sunburn-rash on face and body, remove Femring and contact your healthcare provider.

- 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 examinations 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.

How do I use Femring?

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

2. Estrogens should be used at the lowest dose possible for your treatment only as long as needed. The lowest effective dose of Femring has not been determined. You and your healthcare provider should talk regularly (for example, every 3 to 6 months) about the dose you are using and whether you still need treatment with Femring.



- Femring is inserted into your vagina by you or your healthcare provider.
- Femring should stay in your vagina for 3 months.
- After 3 months Femring should be removed and a new Femring should be inserted.

To insert Femring into your vagina:

1. Wash and dry your hands.
2. Remove Femring from its pouch.
3. Choose the position that is most comfortable for you. For example, lying down or standing with one leg up. (**Diagrams 1a and 1b**, respectively).

DIAGRAM 1a

DIAGRAM 1b

4. Use your thumb and index finger (pointer finger) to press the sides of the ring together. You may find it easier to insert Femring if you twist it into a figure-of-eight shape. (**Diagram 2**)

DIAGRAM 2

5. Use your other hand and hold open the folds of skin around your vagina. (**Diagram 3**)

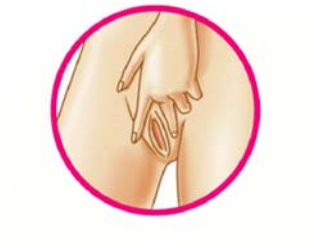


DIAGRAM 3

6. Place the tip of the ring in the vaginal opening and then use your index finger to push the folded ring gently into your vagina. Push it up towards your lower back as far as you can. (**Diagram 4**)

DIAGRAM 4

If the ring feels uncomfortable, you probably did not push it into your vagina far enough. Use your index finger to push the ring as far as you can into your vagina (**Diagram 5**). There is no danger of Femring being pushed too far up in the vagina or getting lost.

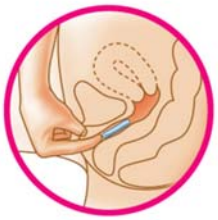


DIAGRAM 5

Femring should now be in your upper vagina (**Diagram 6**). The exact position of Femring in the vagina is not important for it to work.

DIAGRAM 6

7. Wash your hands when you are done.

After 3 months, Femring may no longer release enough medicine to control your menopausal symptoms. To continue to have symptom relief your current Femring should be removed and replaced with a new one if you and your healthcare provider have decided that you still need treatment with Femring.

To remove Femring:

1. Wash and dry your hands.
2. Choose the position that is most comfortable for you (see **Diagrams 1a** and **1b**).
3. Put a finger into your vagina and hook it through the ring. (**Diagram 7**)

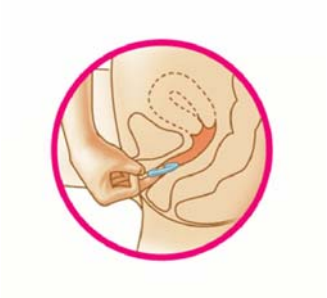


DIAGRAM 7

4. Gently pull downwards and forwards to remove Femring.
5. Wrap the used ring in tissue or toilet paper and put it in a trash can.
6. Wash your hands.

Insert another ring now if your healthcare provider has told you to.

If your Femring comes out of your vagina before 3 months, clean it with warm water and put it back in your vagina.

- Femring can come out if it is not put in far enough.
- Femring can come out when you are pushing hard during a bowel movement.
- Femring can come out if your vaginal muscles are weak.

If Femring comes out often, tell your healthcare provider. Femring may not be right for you.

Call your healthcare provider if you have any problems putting Femring in your vagina or taking it out.

You may leave Femring in place if you need to use medicine for a vaginal infection.

You may leave Femring in place during sex (intercourse). If you take Femring out during intercourse or it comes out, clean it with warm water and put it back in your vagina.

If you lose your Femring, a new Femring should be put in place for 3 months.

General information about safe and effective use of Femring.

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

Keep Femring out of the reach of children.

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

What are the ingredients in Femring?

Femring contains estradiol acetate, an estrogen. It also contains cured silicone elastomer composed of dimethyl polysiloxane silanol, silica (diatomaceous earth), normal propyl orthosilicate, stannous octoate; and barium sulfate. There are no coloring agents in Femring.

Rx only

Manufactured by: Warner Chilcott UK, Ltd., Larne, Northern Ireland, UK
Marketed by: Warner Chilcott (US) Inc., Rockaway, NJ 07866

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REVISED February 2007