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.

CARDIOVASCULAR AND OTHER RISKS

Estrogens with and without progestins should not be used for the prevention of cardiovascular disease.

The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women during 5 years of treatment with conjugated equine estrogens (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg) relative to placebo (see **CLINICAL PHARMACOLOGY, Clinical Studies**). Other doses of conjugated estrogens with medroxyprogesterone acetate, and other combinations of estrogens and progestins were not studied in the WHI and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

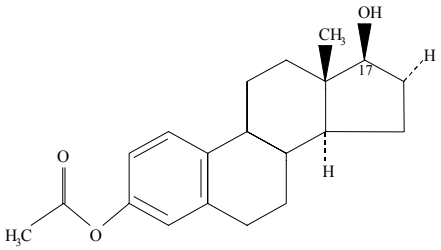
DESCRIPTION

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 systems 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 micrograms of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversions of androstendione, 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 gonadotropins seen in postmenopausal women.

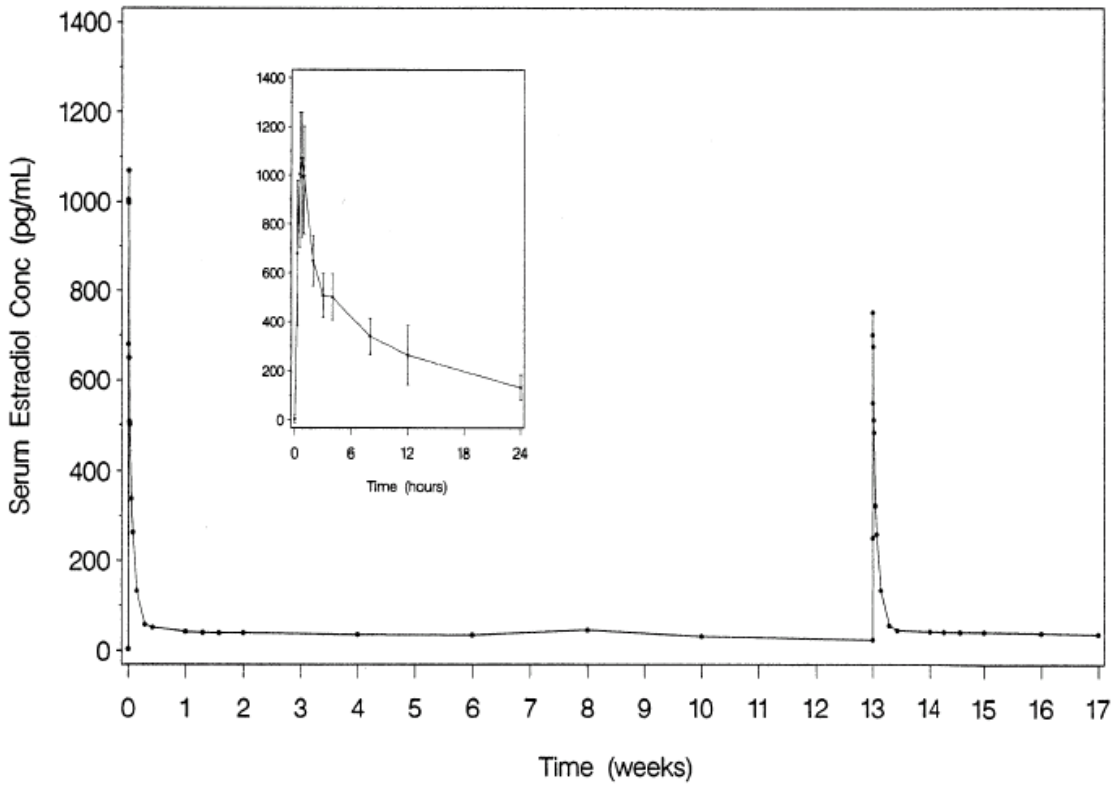
Pharmacokinetics

Estradiol acetate is rapidly hydrolyzed to estradiol.

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)
	Estradiol[2]	12	1665 (23)	0.7 (90)	--[4]
0.10 mg/day	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.

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 blood largely bound to sex hormone binding globulin (SHBG) and albumin.

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 portion 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.

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

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

The CE-only substudy is continuing and results have not been reported. 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 Estrogen/Progestin Substudy of the WHI [a]

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

[a] adapted from JAMA, 2002; 288:321-333.
[b] includes metastatic and non-metastatic breast cancer with the exception of in situ breast cancer.
[c] a subset of the events was combined in a "global index", defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture or death due to other causes.
[d] not included in Global Index.
* nominal confidence intervals unadjusted for multiple looks and multiple comparisons.

For those outcomes included in the "global index", absolute excess risks per 10,000 person-years in the group treated with CE/MPA were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while the absolute risk reductions per 10,000 person-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the "global index" was 19 per 10,000 person-years. There was no difference between the groups in terms of all-cause mortality (See **BOXED WARNINGS**, **WARNINGS**, and **PRECAUTIONS**).

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, other vaginal products should be considered.

CONTRAINDICATIONS

Estrogens should not be used in individuals with any of the following conditions:

1. Undiagnosed abnormal genital bleeding.
2. Known, suspected, or history of cancer of the breast except in appropriately selected patients being treated for metastatic disease.
3. Known or suspected estrogen-dependent neoplasia.
4. Active deep vein thrombosis, pulmonary embolism or a history of these conditions.
5. Active or recent (e.g., within the past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction).
6. Femring should not be used in patients with known hypersensitivity to any of its components.
7. 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 women who have used estrogens and progestins from oral contraceptives inadvertently during early pregnancy. (See **PRECAUTIONS**.)

WARNINGS
See **BOXED WARNINGS**

The use of unopposed estrogens in women who have a uterus is associated with an increased risk of endometrial cancer.

1. Cardiovascular disorders.
Estrogen and estrogen/progestin therapy have 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 cardiovascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hypercholesterolemia and obesity) should be managed appropriately.

a. Coronary heart disease and stroke

In the Women's Health Initiative study (WHI), an increase in the number of myocardial infarctions and stroke has been observed in women receiving CE compared to placebo. These observations are preliminary and the study is continuing. (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 person-years). The increase in risk was observed in year one and persisted.

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

In postmenopausal women with documented heart disease (n = 2,763, average age 66.7 years) a controlled, clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/progestin Replacement Study; HERS), treatment with CE/MPA (0.625 mg/2.5 mg per day) demonstrated no 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 study (WHI), an increase in VTE has been observed in women receiving CE compared to placebo. These observations are preliminary and the study is continuing (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 woman-years in the CE/MPA group compared to 16 per 10,000 woman-years in the placebo group. The increase in VTE risk was observed during the first year and persisted.

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 1 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***.

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

In the WHI, no increased risk of breast cancer in CE-treated women compared to placebo was reported after an average of 5.2 years of therapy. These data are preliminary and that substudy of WHI is continuing.

Epidemiologic studies have reported an increased risk of breast cancer in association with increasing duration of postmenopausal treatment with estrogens with or without a progestin. This association was reanalyzed in

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

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

3. Gallbladder disease.

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

4. 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.

5. 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 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. A possible increased risk of breast cancer

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

c. Impairment of glucose tolerance.

2. ***Elevated blood pressure***.

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

3. ***Familial hyperlipoproteinemia.***

In patients with familial defects of lipoprotein metabolism, 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 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.

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

9. Exacerbation of endometriosis.

Endometriosis may be exacerbated with administration of estrogen therapy.

10. Exacerbation of other conditions.

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

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.

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 for the approved 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 anti-factor 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), T_4 levels (by column or by radioimmunoassay) or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered. Patients with normal thyroid function will be able to compensate for the increased TBG levels, but 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 circulating corticosteroids and sex steroids, respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

4. Increased plasma HDL and HDL_2 cholesterol subfraction concentrations, reduced LDL cholesterol concentration, increased triglyceride levels.

5. Impaired glucose tolerance.

6. Reduced response to metyrapone test.

E. Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver. (See **BOXED WARNINGS**, **CONTRAINDICATIONS,** and **WARNINGS**.)

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

Estrogens should not be used in pregnancy. (See **CONTRAINDICATIONS**.)

G. Nursing Mothers

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

H. Pediatric Use

Femring is not indicated for use in children.

I. Geriatric Use

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

ADVERSE REACTIONS

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

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trial 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 may be related to drug use and for approximate 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 5.

Table 5. 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:

1. Genitourinary system

Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; spotting; 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

Vomiting, abdominal cramps; cholestatic jaundice; increased incidence of gallbladder disease; pancreatitis.

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; steepening of corneal curvature; intolerance to contact lenses.

7. Central nervous system

Migraine; dizziness; mental depression; chorea; nervousness; mood disturbances; irritability; exacerbation of epilepsy.

8. Miscellaneous

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

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of estrogen-containing oral contraceptives 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, 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 limited to the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be reevaluated periodically as clinically appropriate (e.g., 3-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.

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.

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

Distributed by Warner Chilcott Inc., Rockaway, NJ 07866
Manufactured by Galen Ltd., Larne, Northern Ireland, UK

6201G010

PATIENT INFORMATION

(Updated **FULL DATE HERE**)

Femring™ (estradiol acetate vaginal ring)

This leaflet describes the risks and benefits of treatment with Femring. Read this information carefully before you start using Femring. Read the information 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 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 using Femring. 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. 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.

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 intense episodes of heat and sweating ("hot flashes" or "hot flushes"). In some women the symptoms are mild and they will not need to take estrogens. In other women, symptoms can be more severe. You and your healthcare provider should talk regularly about whether you still need treatment with Femring.

- **treat moderate to severe dryness, itching and burning in or around the vagina.** You and your healthcare provider should talk regularly about whether you still need treatment with Femring to control these problems.

Who should not use Femring?
Do not use 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 have 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.**
- **are allergic to any of the components in Femring. See the end of this leaflet for a list of all the components 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 your medical problems.** Your healthcare provider may need to check you more carefully if you have certain conditions, such as asthma (wheezing), epilepsy (seizures), migraine, endometriosis or problems with your heart, liver, thyroid, kidneys or have high calcium levels in your blood.
- **about all the medicines you take.** 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
- Change 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 other unusual symptoms that concern you.

Common side effects include:
- Headaches
- Breast pain
- Irregular vaginal bleeding or spotting
- Stomach/abdominal cramps, bloating
- Nausea and vomiting
- Hair loss

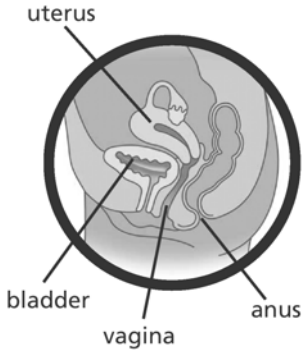
Other side effects include:
- High blood pressure
- Liver problems
- High blood sugar
- Fluid retention
- Enlargement of benign tumors of the uterus ("fibroids")
- Vaginal yeast infections

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 having a serious side effect with Femring?

- Talk with your healthcare provider about whether you should continue using Femring.
- See your healthcare provider right away if you get vaginal bleeding while using Femring.
- 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.

How do I use 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 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**)

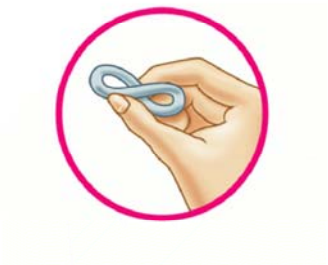


DIAGRAM 2

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

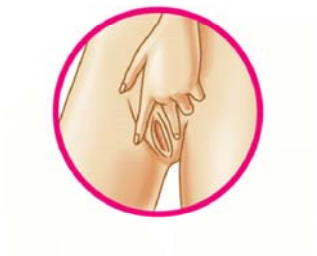


DIAGRAM 3

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**)

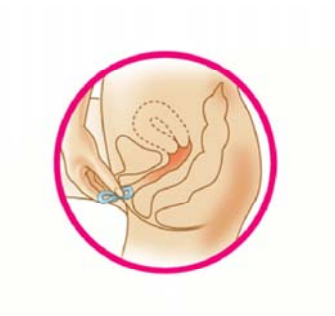


DIAGRAM 4

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.

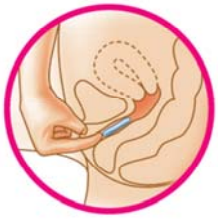


DIAGRAM 5

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.

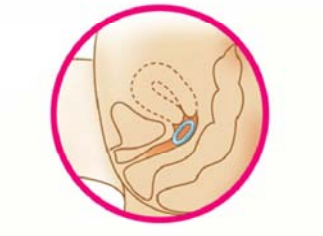


DIAGRAM 6

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**)

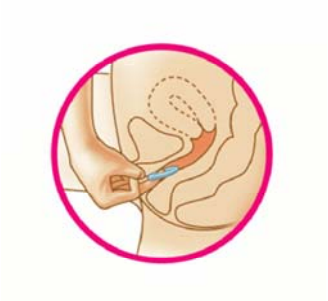


DIAGRAM 7

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 a condition for which it was not prescribed. Do not give Femring to other people, even if they have the same symptoms that 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 also get more information by calling the toll free number 800-521-8813.

What are the components 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.

Distributed by Warner Chilcott Inc., Rockaway, NJ 07866
Manufactured by Galen Ltd., Larne, Northern Ireland, UK

6201G020