

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-813

LABELING

ELESTRIN™

(estradiol gel)

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 Women’s Health Initiative (WHI) estrogen alone substudy 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 WHI substudy reported increased risk 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 the WHI study, 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**.)

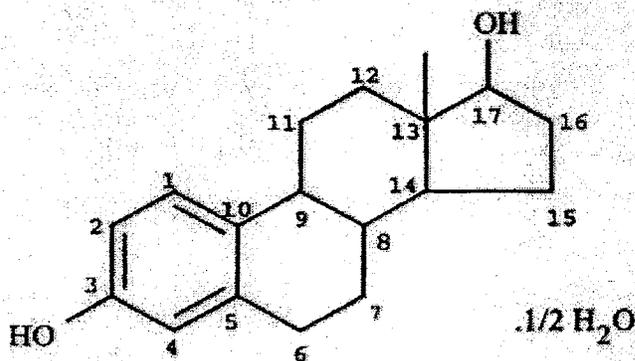
Other doses of conjugated equine estrogens with medroxyprogesterone acetate and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens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

Elestrin™ (estradiol gel) contains 0.06% estradiol in a hydroalcoholic gel base. The gel is applied onto the skin in a thin layer. The recommended area of application is the upper arm to shoulder (approximately 320 cm²). One pump actuation delivers Elestrin in a unit dose of 0.87 g, which contains 0.52 mg of estradiol. The 0.87 g dose provides systemic delivery of 0.0125 mg of estradiol daily. The 1.7 g dose, two pump actuations, provides systemic delivery of 0.0375 mg daily.

Estradiol is a white crystalline powder, chemically described as estra-1,3,5(10)-triene-3,17-diol, (17β)-. It has a molecular formula of C₁₈H₂₄O₂·¹/₂H₂O and molecular weight of 281.4.

The structural formula is:



The active component of Elestrin is estradiol. The remaining components of the gel (ethanol, propylene glycol, diethylene glycol monoethyl ether, carbomer 940, triethanolamine, edetate disodium, and purified water) are pharmacologically inactive.

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

A. Absorption

Steady-state serum concentrations of estradiol are achieved in approximately 3 days following daily application of Elestrin to the upper arm.

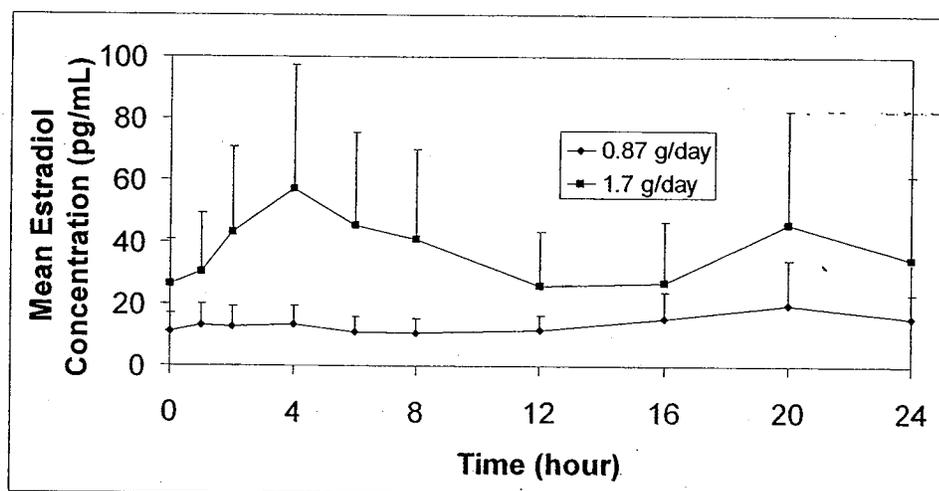
Pharmacokinetic parameters for estradiol on Day 14 following daily application of 0.87 g or 1.7 g of Elestrin are summarized in Table 1. The nominal mean delivery rates of estradiol using the baseline-adjusted average serum concentrations from pharmacokinetic studies using 0.87 g/day and 1.7 g/day are 0.012 mg/day and 0.041 mg/day, respectively.

Table 1 Summary of Unadjusted PK Parameters for Estradiol after 14 Days of Dosing		
Pharmacokinetic Parameter	0.87 g Elestrin (0.52 mg/d Estradiol) Mean	1.7 g Elestrin (1.04 mg/d Estradiol) Mean
AUC ₀₋₂₄ (pg hr/mL)	335.2	940.2
C _{max} (pg/mL)	21.6	66.7
C _{ave} (pg/mL)	15.4	39.2
C _{min} (pg/mL)	9.4	21.1
T _{max} (h) ^a	18 (1 – 20)	4 (1 – 20)
Fluctuation Index	0.80	1.16
E ₂ :E ₁ ratio	0.53	0.98

^a T_{max} shown as median (range)

Mean concentrations of estradiol over a 24-hour period on Day 14 are shown in Figure 1.

Figure 1 Mean Serum Estradiol Concentrations (Unadjusted) After Multiple Doses. Error bars represent standard deviations.



Mean unadjusted serum estradiol concentrations for 0.87 g/day (◆◆); and 1.7 g/day (⊖■)

Application of sunscreen 10 minutes before application of Elestrin increased the exposure to estradiol by approximately 55%. No significant change in estradiol exposure was observed when sunscreen was applied 25 minutes after application of Elestrin. In the same study, prolonged (7 days) concomitant application of sunscreen to the site of Elestrin application increased exposure to estradiol by about 2-fold, regardless of whether it was applied before or after application of Elestrin.

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

Elestrin has been studied only in postmenopausal women. No pharmacokinetic studies were conducted in special populations, including patients with renal or hepatic impairment or any other special populations.

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

result in side effects.

G. Estradiol Transfer

The potential for estradiol transfer between treated postmenopausal female subjects and their untreated male partners was evaluated. Two and 8 hours after women applied 2.6 g Elestrin to one arm (12 women per time point), they engaged in direct arm-to-arm contact with a male partner for 5 minutes. No significant changes in estradiol pharmacokinetic parameters were observed in the male partners after contact.

Less than 10% of the estradiol dose was measured on the skin at 2 and 8 hours after application. After washing the application site with soap and water at 8 hours after application, about 1% of the dose of estradiol was measurable.

CLINICAL STUDIES

Effects On Vasomotor Symptoms

A randomized, double-blind, placebo-controlled clinical trial evaluated the efficacy of 12-week treatment with three different daily doses of Elestrin for the treatment of vasomotor symptoms in 484 postmenopausal women between 28 and 74 years of age (mean 54 years; 83-88% Caucasian per group) who had at least 60 moderate-to-severe hot flushes per week at baseline. Subjects applied placebo, Elestrin 0.87 g (0.52 mg estradiol), 1.7 g (1.02 mg estradiol), or 2.6 g (1.56 mg estradiol) once daily to the upper arm. Reduction in both the frequency and severity of moderate-to-severe hot flushes was statistically significant for the Elestrin 1.7 g/day dose compared to placebo at week 4. Statistically significant reductions in both the frequency and severity of moderate-to-severe hot flushes when compared to placebo were delayed for the Elestrin 0.87 g/day dose to week 5. Both the 0.87 g/day and 1.7 g/day doses were statistically significant compared to placebo at week 12. The reductions in frequency and severity are shown in Table 2.

Evaluation	Placebo (N=137)	Elestrin 0.87 g/day (N=136)	Elestrin 1.7 g/day (N=142)
Number of Daily Hot Flashes			
Baseline (Mean ± SD) ^b	13.5 ± 4.5	13.3 ± 4.6	13.1 ± 6.5
Mean Change: Week 4	-5.1	-6.5 #	-8.0***
Week 5	-5.1	-7.5*	-8.8***
Week 12	-5.4	-8.5***	-10.0**
Daily Hot Flush Severity^c			
Baseline (Mean ± SD) ^b	2.4 ± 0.3	2.4 ± 0.3	2.4 ± 0.3
Mean Change: Week 4	-0.2	-0.5 #	-0.7***
Week 5	-0.2	-0.5*	-0.8***
Week 12	-0.3	-0.8***	-1.2***

^a Differences from baseline based on LS means derived from the ANCOVA model with factors for baseline, treatment, site, and treatment-by-baseline interaction.

^b Unadjusted means and standard deviations, based on the first 14 days of the Screening Period.

^c Severity score: 1=mild, 2=moderate, 3=severe.

SD: standard deviation

#P= ns, *P<0.01, **P<0.001, ***P<0.0001 for treatment comparison with placebo (Dunnett's test).

Women's Health Initiative Studies

The Women's Health Initiative (WHI) enrolled approximately 27,000 predominantly healthy postmenopausal women to assess the risks and benefits of either the use of oral conjugated estrogens (CE 0.625 mg) alone per day or in combination with medroxyprogesterone acetate (MPA 2.5 mg) 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 the estrogen plus progestin substudy), 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. 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 3.

Table 3 RELATIVE AND ABSOLUTE RISK SEEN IN THE ESTROGEN-ALONE SUBSTUDY OF WHI ^a			
Event	Relative Risk CE vs. Placebo (95% nCI ^b)	Placebo n = 5,429	CE n = 5,310
		Absolute Risk per 10,000 Women-Years	
CHD events ^c	0.95 (0.79-1.16)	56	53
<i>Nonfatal MI^c</i>	0.91 (0.73-1.14)	43	40
<i>CHD death^c</i>	1.01 (0.71-1.43)	16	16
Invasive breast cancer ^c	0.80 (0.62-1.04)	34	28
Stroke ^d	1.39 (1.10-1.77)	32	44
Deep vein thrombosis ^{c,e}	1.47 (1.06-2.06)	15	23
Pulmonary embolism ^c	1.37 (0.90-2.07)	10	14
Colorectal cancer ^d	1.08 (0.75-1.55)	16	17
Hip fracture ^d	0.61 (0.41-0.91)	17	11
Vertebral fractures ^{d,e}	0.62 (0.42-0.93)	17	11
Total fractures ^{d,e}	0.70 (0.63-0.79)	195	139
Death due to other causes ^{d,f}	1.08 (0.88-1.32)	50	53
Overall mortality ^{d,e}	1.04 (0.88-1.22)	78	81
Global index ^{d,g}	1.01 (0.91-1.12)	190	192

^a Adapted from *JAMA* 2004;291:1701-1712

^b Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.

^c Results are based on centrally adjudicated data for an average follow-up of 7.1 years.

^d Results are based on an average follow-up of 6.8 years.

^e Not included in Global Index.

^f All deaths, except from breast or colorectal cancer, definite/probable CHD, PE or cerebrovascular disease.

^g 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.

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 0.625 mg alone were 12 more strokes, while the absolute risk reduction per 10,000 women-years was 6 fewer hip fractures. The absolute excess risk of events included in the "global index" was a nonsignificant 2 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**.)

The CE/MPA substudy was also stopped early because, according to 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, 6.8% Black, 5.4% Hispanic, 3.9% Other) after an average follow-up of 5.6 years, are presented in Table 4:

Event ^c	Relative Risk CE/MPA vs. Placebo (95% nCI ^b)	Placebo n = 8102	CE/MPA n = 8506
		Absolute Risk per 10,000 Women-Years	
CHD events	1.24 (1.00-1.54)	33	39
<i>Non-fatal MI</i>	1.28 (1.00-1.63)	25	31
<i>CHD death</i>	1.10(0.70-1.75)	8	8
Invasive breast cancer ^c	1.24 (1.01-1.54)	33	41
All Stroke	1.31 (1.02-1.68)	24	31
<i>Ischemic Stroke</i>	1.44 (1.09-1.90)	18	26
Deep vein thrombosis	1.95 (1.43-2.67)	13	26
Pulmonary embolism	2.13 (1.45-3.11)	8	18
Invasive colorectal cancer	0.56 (0.38-0.81)	16	9
Endometrial cancer	0.81 (0.48-1.36)	7	6
Cervical cancer	1.44 (0.47-4.42)	1	2
Hip fracture	0.67(0.47-0.96)	16	11
Vertebral fractures	0.65 (0.46-0.92)	17	11
Lower arm/wrist fractures	0.71 (0.59-0.85)	62	44
Total fractures	0.76 (0.69-0.83)	199	152

^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.

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 6 more CHD events, 7 more strokes, 10 more PEs, and 8 more invasive breast cancers, while the absolute risk reductions per 10,000 women-years were 7 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the “global index” was 19 per 10,000 women-years (RR 1.15, 95% nCI 1.03-1.28). (See **BOXED WARNINGS, WARNINGS, and PRECAUTIONS.**)

Women’s Health Initiative Memory Study

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

After an average follow-up of 5.2 years, 28 women in the CE-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 CE-alone group was 1.49 (95% confidence interval [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 CE/MPA 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 conjugated estrogens (CE 0.625 mg) plus medroxyprogesterone acetate (MPA 2.5 mg) on the incidence of probable dementia (primary outcome) compared with placebo.

After an average follow-up of 4 years, 40 women in the CE/MPA 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, 1.21-3.48) 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 WARNING and WARNINGS, Dementia, and PRECAUTIONS, Geriatric Use.**)

INDICATIONS AND USAGE

Elestrin 0.87 g/day and 1.7 g/day are indicated in the:

Treatment of moderate-to-severe vasomotor symptoms associated with menopause.

CONTRAINDICATIONS

Estrogen products, including Elestrin, 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. Known hypersensitivity to the ingredients of Elestrin.
8. Known or suspected pregnancy. There is no indication for Elestrin 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 events 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 VTE (e.g., personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

a. Stroke

In the WHI estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women receiving CE 0.625 mg daily compared to placebo (44 versus 32 per 10,000 women-years). The increase in risk was observed in year 1 and persisted. (See **CLINICAL STUDIES**.)

In the CE/MPA substudy of WHI, a statistically significant increased risk of stroke was reported in women receiving CE/MPA daily compared to women receiving placebo (31 versus 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 nonfatal myocardial infarction (MI), silent MI and CHD death) 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 versus 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/2.5 mg per day) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE/MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE/MPA-treated group than in the placebo group in year 1, but not during the subsequent years.

Participation in an open label extension of the original HERS trial (HERS II) was agreed to by 2,321 women. 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 equine 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 risk 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 receiving CE compared to placebo (30 versus 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first two years. (See **CLINICAL STUDIES**.)

In the CE/MPA substudy of WHI, a statistically significant two-fold greater rate of VTE was reported in women receiving CE/MPA compared to women receiving placebo (35 versus 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women-years) and PE (18 versus 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was observed during the first year and persisted. (See **CLINICAL STUDIES**.)

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 by 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 times greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk appears associated with

prolonged use, with an increased risk of 15- to 24-fold for 5 to 10 years or more. 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.

In a 12-week clinical trial, one case of complex hyperplasia with atypia was reported in the Elestrin 1.7 g/ day dose.

b. Breast Cancer

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

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).

The CE/MPA substudy of WHI study reported an increased risk of breast cancer in women who took CE/MPA for a mean follow-up of 5.6 years. Observational studies have also reported an increased risk for estrogen/progestin combination therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. In the WHI trial and from observational studies, the excess risk increased with duration of use. From observational studies, the risk appeared to return to baseline in about 5 years after stopping treatment. In addition, observational studies suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen/progestin combination therapy as compared to estrogen-alone therapy.

In the CE/MPA substudy, 26% of the women reported prior use of estrogen-alone and/or estrogen/progestin combination hormone therapy. After a mean follow-up of 5.6 years during the clinical trial, the relative risk of invasive breast cancer was 1.24 (95% nCI, 1.01-1.54), and the absolute risk was 41 versus 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 versus 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 versus 36 cases per 10,000 women-years, for CE/MPA compared with placebo. In the same substudy, invasive breast cancers were larger and diagnosed at a more advanced stage in the CE/MPA group compared with the placebo group. Metastatic disease was rare with no apparent difference between the two groups. Other prognostic factors such as histologic subtype, grade and hormone receptor status did not differ between the groups.

The use of estrogen 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 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 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, a population of 4,532 postmenopausal women aged 65 to 79 years was randomized to CE/MPA (0.625mg/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 estrogen alone versus placebo was 1.49 (95% CI, 0.83-2.66). The absolute risk of probable dementia for estrogen-alone versus placebo was 37 versus 25 cases per 10,000 women-years. It is unknown whether these findings apply to younger postmenopausal women. (See **CLINICAL STUDIES** and **PRECAUTIONS, Geriatric Use.**)

In the estrogen plus progestin substudy, after an average follow-up of 4 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 versus placebo was 2.05 (95% CI, 1.21-3.48). The absolute risk of probable dementia for CE/MPA versus placebo was 45 versus 22 cases per 10,000 women-years. (See **CLINICAL STUDIES** and **PRECAUTIONS, Geriatric Use.**)

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 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 past history of cholestatic jaundice

Estrogens may be poorly metabolized in patients with impaired liver function. For patients with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised, and in the case of recurrence, medication should be discontinued.

5. Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T₄ and T₃ serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored to maintain their free thyroid hormone levels in an acceptable range.

6. Fluid retention

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

7. Hypocalcemia

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

8. Ovarian cancer

The CE/MPA substudy of WHI study reported that after an average follow-up of 5.6 years, the relative risk for ovarian cancer for estrogen plus progestin versus placebo was 1.58 (95% nCI, 0.77 – 3.24) but was not statistically significant. The absolute risk for estrogen plus progestin 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 10 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

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

11. Photosensitivity/Photoallergy

Increased sensitivity to direct exposure to the sun on areas of Elestrin application has not been evaluated.

12. Sunscreen application

Estradiol absorption was increased when sunscreen was applied 10 minutes before Elestrin application. Sunscreen should not be applied to the same site until at least 25 minutes after the application of Elestrin.

Concomitant application of sunscreen and Elestrin to the same application site for 7 or more days may increase estradiol absorption. Avoid applying sunscreen to the area of Elestrin application for extended period of 7 or more days. (See **CLINICAL PHARMACOLOGY, Absorption.**)

13. Miscellaneous

Alcohol based gels potentially are flammable. Avoid fire, flame, or smoking until the gel has dried.

B. Information for Patients

Physicians are advised to discuss the Patient Information leaflet with patients for whom they prescribe Elestrin.

C. Laboratory Tests

Estrogen administration should be initiated at the lowest dose approved for the treatment of postmenopausal moderate to severe vasomotor symptoms 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), 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], SHBG), leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

4. Increased plasma HDL and HDL₂ cholesterol subfraction concentrations, reduced LDL cholesterol concentration, increased triglycerides levels.

5. Impaired glucose tolerance.

6. Reduced response to metyrapone test.

E. Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term continuous administration of estrogen, with or without progestin, in women with or 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.

F. Pregnancy

Estrogen products, including Elestrin, 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 estrogen products, including Elestrin, are administered to a nursing woman.

H. Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

I. Geriatric Use

Clinical studies of Elestrin did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

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

In the estrogen-alone substudy of the WHIMS, a population of 2,947 hysterectomized women, aged 65 to 79 years, was randomized to estrogen alone (CE 0.625 mg) or placebo. After an average follow-up of 5.2 years, the relative risk (CE versus 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 versus 25 cases per 10,000 women-years.

Of the total number of subjects in the CE/MPA substudy of the WHI, 44% (n = 7,320) were 65 years and older, while 6.6% (n = 1,095) were 75 years and older. There was a higher relative risk (CE/MPA versus placebo) of non-fatal stroke and invasive breast cancer in women 75 and older 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 versus 24 per 10,000 women-years and 52 versus 12 per 10,000 women years, respectively.

In the estrogen plus progestin substudy of WHIMS, a population of 4,532 postmenopausal women, aged 65 to 70 years, was randomized to conjugated estrogens (CE 0.625 mg) plus medroxyprogesterone acetate (MPA 2.5 mg) or placebo. In the estrogen plus progestin group, after an average follow-up of 4 years, the relative risk (CE/MPA versus 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 versus 22 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 **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.

Elestrin was studied in a placebo-controlled trial that included a total of 484 postmenopausal women. The adverse events that occurred at a rate greater than 5% in any of the treatment groups are summarized in Table 5.

Body System / Signs and Symptoms	Number (%) of Subjects		
	Placebo (n=137)	Elestrin 0.87 g/day (n=136)	Elestrin 1.7 g/day (n=142)
Gastrointestinal disorders			
Nausea	2 (1.5)	6 (4.4)	4 (2.8)
General disorders & administrative site conditions			
Edema peripheral	0 (0)	1 (0.7)	0 (0)
Reproductive system & breast disorders			
Breast tenderness	5 (3.6)	9 (6.6)	11 (7.7)
Metrorrhagia	3 (2.2)	6 (4.4)	13 (9.2)
Vaginal discharge	1 (0.7)	2 (1.5)	5 (3.5)
Nipple pain	0 (0)	1 (0.7)	3 (2.1)
Endometrial hyperplasia	0 (0)	0 (0)	1 (0.7)
Respiratory, thoracic & mediastinal disorders			
Nasopharyngitis	10 (7.3)	14 (10.3)	12 (8.5)
Upper respiratory tract infection	5 (3.6)	8 (5.9)	5 (3.5)

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

1. Genitourinary system

Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding; spotting; dysmenorrhea; increase in size of uterine leiomyomata; vaginitis, including vaginal candidiasis; change in amount of cervical secretion; changes in cervical ectropion; ovarian cancer; endometrial hyperplasia; endometrial cancer.

2. Breasts

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

3. Cardiovascular

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

4. Gastrointestinal

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

5. Skin

Chloasma or melasma that may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; pruritus, 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; arthralgias; leg cramps; changes in libido; urticaria, angioedema, anaphylactoid/anaphylactic reactions; hypocalcemia; exacerbation of asthma; increased triglycerides.

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of estrogen-containing 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 re-evaluated 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.

Elestrin is applied once daily to the upper arm for the treatment of moderate to severe vasomotor symptoms associated with the menopause using a metered-dose pump which delivers 0.87 gram of estradiol gel per actuation.

Patients should be started with the lowest effective dose of Elestrin, which is one pump per day (0.87 g/day, which contains 0.52 mg of estradiol).

Subsequent dosage adjustment may be made based upon the individual patient response. This dose should be periodically reassessed by the healthcare provider.

HOW SUPPLIED

Elestrin is estradiol 0.06% in a colorless, non-staining hydroalcoholic gel supplied in a non-aerosol, metered-dose pump container constructed of polypropylene. The drug product is contained within a collapsible inner liner/bag consisting of an inner and outer layer of low density polyethylene with a resealable polypropylene cap. Each individually packaged pump contains 144 g of gel and is capable of delivering 100 metered doses of approximately 0.87 g of drug product per pump actuation.

Keep out of reach of children.

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature].

Elestrin™ is a trademark of BioSante Pharmaceuticals, Inc., Lincolnshire, Illinois, 60069.

Manufactured for:

Kenwood Therapeutics

A Division of Bradley Pharmaceuticals, Inc.

Fairfield, NJ 07004-2402 USA

www.Bradpharm.com

www. Bradpharm.com

Manufactured by:

DPT Laboratories, Ltd.

San Antonio, TX 78215

PATIENT INFORMATION

(Updated December 14, 2006)

Elestrin™

(estradiol gel)

By prescription only

Read this Patient Information leaflet before you start using Elestrin™ and read what you get each time you refill your Elestrin prescription. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition and your treatment.

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT ELESTRIN (AN ESTROGEN HORMONE)?

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

Report any unusual vaginal bleeding right away while you are using Elestrin. 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.

- Do not use estrogens with or without progestins to prevent dementia
- 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 Elestrin.

What is Elestrin?

Elestrin is a medicine in a colorless gel that contains an estrogen hormone (estradiol) which is absorbed through the skin into the bloodstream.

What is Elestrin used for?

Elestrin 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 Elestrin.

Who should not use Elestrin?

Do not start using Elestrin 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 Elestrin.

- **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 Bio-E-Gel or any of its ingredients**

See the end of this leaflet for a list of ingredients in Elestrin.

- **Think you may be pregnant**

Tell your healthcare provider:

- **If you are breastfeeding**

The hormone in Elestrin 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, 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 Elestrin works. Elestrin 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 using Elestrin.

What are the ingredients in Elestrin?

Active ingredient: estradiol.

Inactive ingredient: purified water, ethanol, propylene glycol, diethylene glycol monoethyl ether, carbomer 940, triethanolamine, and edetate disodium.

How should I use Elestrin?

1. Start at the lowest dose and talk to your healthcare provider about how well that dose is working for you.
2. Elestrin should be used at the lowest dose possible for your treatment and only as long as needed. You and your healthcare provider should talk regularly (for example, every 3 to 6

months) about the dose you are taking and whether you still need treatment with Elestrin.

Elestrin comes in a metered-dose pump. One dose of Elestrin is released each time the pump is depressed (pressed down).

Use Elestrin exactly how your healthcare provider tells you.

The Elestrin pump contains enough of the medicine to let you prime the pump before you use it the first time (ten depressions) and then use the pump a total of 100 times (100 depressions) as prescribed by your healthcare provider. After you have initially primed the pump with ten pump depressions and have used a total of 100 doses of Elestrin, you will need to throw the pump away and use a new one. The correct amount of medicine in each dose cannot be assured after 100 doses have been used, even though the pump container is not completely empty.

Important things to remember when using Elestrin

Wash your hands with soap and water after applying the gel to reduce the chance that the medicine will be spread from your hands to other people.

Allow the gel to dry for five minutes or more before dressing. Try to keep the area dry for as long as possible.

Do not allow others to come in contact with the area of skin where you applied the gel for at least two hours after you apply Elestrin.

Always move the spout into locked position and place the cap over the top of the pump after each use.

Never apply Elestrin to the breast. Never apply Elestrin in or around the vagina.

Do not allow others to apply the gel for you.

Do not apply sunscreen to the area where the gel was applied for at least 25 minutes.

Do not apply sunscreen to the area where the gel was applied for 7 or more consecutive days.

Avoid fire, flame or smoking until the gel has dried. Elestrin contains alcohol. Alcohol based gels are flammable.

It is important that you read and follow the detailed “Patient Instructions for Use” at the

end of this leaflet on how to use the Elestrin pump and apply the dose.

What should I do if someone else is exposed to Elestrin?

If someone else is exposed to Elestrin by direct contact with the gel, that person should wash the area of contact with soap and water as soon as possible. The longer the gel is in contact with the skin before washing, the greater is the chance that the other person will absorb some of the estrogen hormone. This is especially important for men and children.

What should I do if I get Elestrin in my eyes?

If you get Elestrin in your eyes, rinse your eyes right away with warm clean water to flush out any Elestrin. Seek medical attention if needed.

What should I do if I miss a dose?

If you miss a dose, do not double the dose on the next day to catch up. If your next dose is less than 12 hours away, it is best just to wait and apply your normal dose the next day. If it is more than 12 hours until the next dose, apply the dose you missed and resume your normal dosing the next day.

What are the possible side effects of estrogens?

Less common but serious side effects include:

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

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

- Breast lumps

- Unusual vaginal bleeding
- Dizziness and faintness
- Changes in speech
- Severe headaches
- Chest pain
- Shortness of breath
- Pains in your legs
- Changes in vision
- Vomiting

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

Common side effects include:

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

Other side effects include:

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

- Vaginal yeast infection

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

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

Talk with your healthcare provider regularly about whether you should continue using Elestrin. If you have a uterus, talk to your healthcare provider about whether the addition of a progestin is right for you. In general, the addition of a progestin is recommended for women with a uterus to reduce the chance of getting cancer of the uterus. See your healthcare provider right away if you get vaginal bleeding while using Elestrin. 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 a higher chance for getting heart disease. Ask your healthcare provider for ways to lower your chances of getting heart disease.

Have an annual gynecologic exam

General information about safe and effective use of Elestrin

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

Keep Elestrin out of the reach of children

This leaflet provides a summary of the most important information about Elestrin. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about Elestrin that is written for health professionals. You can get more information by calling the toll free number (*add number here*).

Patient Instructions for Use.

- 1. Remove the cap.**
- 2. Activate the pump.**

- Unlock the pump by turning the spout on top of the bottle a quarter turn to the left or the right

3. Prime the pump before using the pump for the first time

- Prime the pump by fully depressing the spout ten (10) times.
- Throw away the unused gel by placing it in the trash to avoid another person or pet from accidental contact with the gel or, eating or drinking it.
- **After priming, the pump is ready to use**

One complete pump depression will dispense the same amount of Elestrin each time.

After each daily dose, return the spout to the locked position and replace the cap before you put it away.

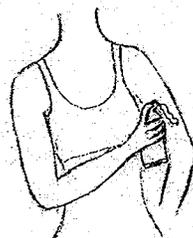
4. Apply Elestrin.

- **Dry skin completely before applying Elestrin.**

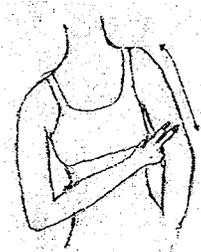
You should apply your daily dose of gel to clean, dry, unbroken skin. If you take a bath or shower or use a sauna, apply Elestrin after your bath, shower, or sauna. If you go swimming, try to leave as much time as possible, at least 2 hours, between applying your Elestrin dose and going into the water.

- **Apply Elestrin at the same time each day.**

To apply the dose, hold the pump with the tip facing the application area of the arm. For each pump depression needed, press the pump firmly and fully with a continuous motion without hesitation.



Gently spread the gel using only 2 fingers. Spread and gently rub in the gel over the entire area of your upper arm and shoulder area, as illustrated.



5. Wash your hands with soap and water.

Elestrin should not be used after the date printed on the end of the metered-dose pump after the term "Exp." (expiration date).

Elestrin™ is a trademark of BioSante Pharmaceuticals, Inc., Lincolnshire, Illinois, 60069.

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Kenwood Therapeutics

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Fairfield, NJ 07004-2402 USA

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35 page(s) of draft
labeling has been
removed from this
portion of the review.