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EstroGel® 0.06%
(estradiol gel)

℞ only

ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER

Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of "natural" estrogens results in a different endometrial risk profile than synthetic estrogens at equivalent estrogen doses. (See **WARNINGS, Malignant neoplasms, *Endometrial cancer***.)

CARDIOVASCULAR AND OTHER RISKS

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

The estrogen-alone substudy of the Women's Health Initiative (WHI) reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (aged 50-79 years) during 6.8 and 7.1 years, respectively, of treatment with oral conjugated estrogens (CE 0.625 mg) per day, relative to placebo. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular disorders**.)
The estrogen-plus-progestin substudy of the WHI reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (aged 50-79 years) during 5.6 years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) per day relative to placebo. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular disorders** and **Malignant neoplasms, *Breast cancer***.)

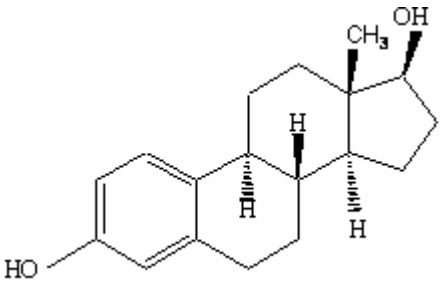
The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with CE 0.625 mg alone and during 4 years of treatment with CE 0.625 mg combined with MPA 2.5 mg, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See **CLINICAL STUDIES** and **WARNINGS, Dementia**, **and PRECAUTIONS, Geriatric Use**.)
Other doses of conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins, were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

DESCRIPTION

EstroGel® (estradiol gel) contains 0.06% estradiol in an absorptive hydroalcoholic gel base formulated to provide a controlled release of the active ingredient. The gel is applied over a large area (750 cm^2)

of the skin in a thin layer. The recommended area of application is the arm, from wrist to shoulder. An EstroGel unit dose of 1.25 g contains 0.75 mg of estradiol.

Estradiol is a white crystalline powder, chemically described as estra-1,3,5(10)-triene-3,17β-diol. It has an empirical formula of $C_{18}H_{24}O_2$ and molecular weight of 272.39. The structural formula is:



The active component of the transdermal gel is estradiol. The remaining components of the gel (purified water, alcohol, triethanolamine and carbomer 934P) are pharmacologically inactive.

CLINICAL PHARMACOLOGY

EstroGel provides systemic estrogen replacement therapy by releasing estradiol, the major estrogenic hormone secreted by the human ovary.

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, 2 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 elevated levels of these hormones seen in postmenopausal women.

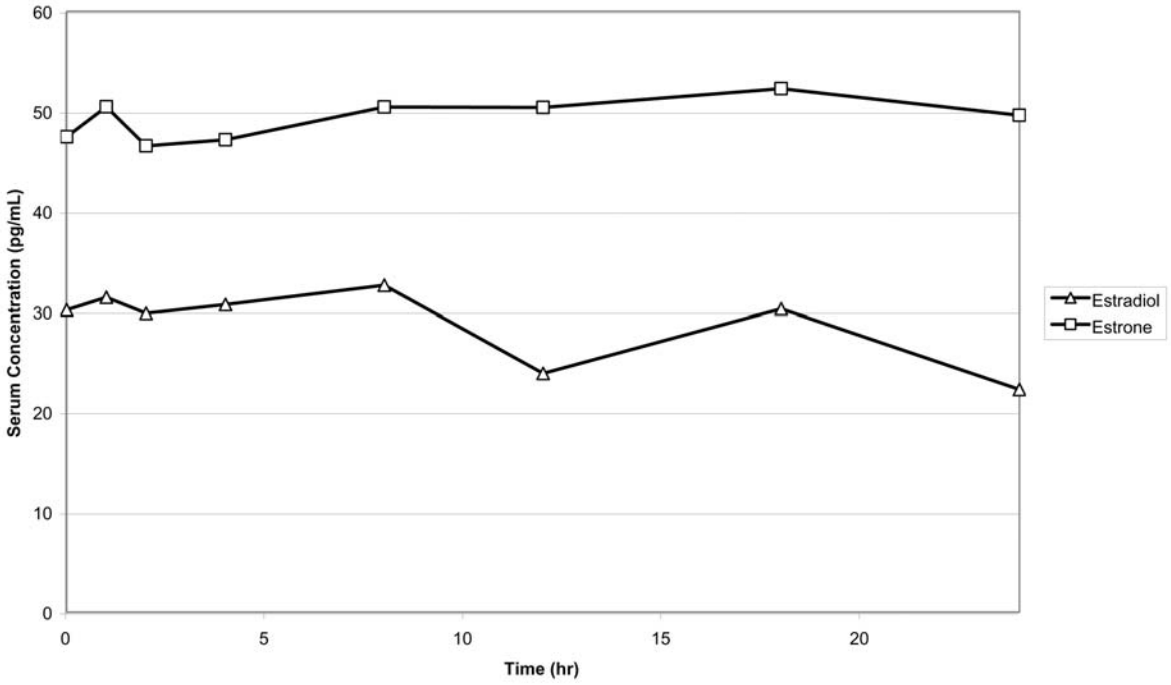
Pharmacokinetics

A. Absorption

Estradiol is transported across intact skin and into the systemic circulation by a passive diffusion process. The rate of diffusion across the stratum corneum is the rate-limiting factor. When EstroGel is applied to the skin, it dries in 2 to 5 minutes.

EstroGel 1.25 g was administered to 24 postmenopausal women once daily on the posterior surface of 1 arm from wrist to shoulder for 14 consecutive days. Mean maximal serum concentrations of estradiol and estrone on day 14 were 46.4 pg/mL and 64.2 pg/mL, respectively. The time-averaged serum estradiol and estrone concentrations over the 24-hour dose interval after administration of 1.25 g EstroGel on day 14 are 28.3 pg/mL and 48.6 pg/mL, respectively. Mean concentration-time profiles for unadjusted estradiol and estrone on day 14 are shown in Figure 1.

FIGURE 1
Mean Serum Concentration-time Profiles for Unadjusted Estradiol and Estrone After Multiple-dose Applications of 1.25 g EstroGel for 14 Days



The serum concentrations of estradiol following 2.5-g EstroGel applications (1.25 g on each arm from wrist to shoulder) appeared to reach steady state after the third daily application.

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, the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women, a significant proportion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens. Although the clinical significance has not been determined, estradiol from EstroGel does not go through first-pass liver metabolism.

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

The apparent terminal exponential half-life for estradiol was about 36 hours following administration of 1.25 g EstroGel.

E. Special populations
EstroGel has been studied only in postmenopausal women. No pharmacokinetic studies were conducted in special populations, including patients with renal or hepatic impairment.

F. Drug interactions
No clinical drug-drug interaction studies have been conducted with EstroGel.

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 estrogen and may result in side effects.

G. Potential for estradiol transfer and effects of washing
The effect of estradiol transfer was evaluated in 24 healthy postmenopausal women who topically applied 1.25 g of EstroGel once daily on the posterior surface of 1 arm from wrist to shoulder for a period of 14 consecutive days. On each day, 1 hour after gel application, a cohort of 24 non-dosed healthy postmenopausal females directly contacted the dosed cohort at the site of gel application for 15 minutes. No change in endogenous mean serum concentrations of estradiol was observed in the non-dosed cohort after direct skin-to-skin contact with subjects administered EstroGel.

The effect of application site washing on the serum concentrations of estradiol was determined in 24 healthy postmenopausal females who applied 1.25 g of EstroGel once daily for 14 consecutive days. Site washing 1 hour after the application resulted in a 22% mean decrease in average 24-hour serum concentrations of estradiol.

CLINICAL STUDIES

Effects on vasomotor symptoms
In a placebo-controlled study, 145 postmenopausal women between 29 and 67 years of age (81.4% were White) were randomly assigned to receive 1.25 g of EstroGel (containing 0.75 mg of estradiol) or placebo gel for 12 weeks. Efficacy was assessed at 4 and 12 weeks of treatment. A statistically significant reduction in the frequency and severity of moderate to severe hot flushes was shown at weeks 4 and 12. (See Table 1.)

TABLE 1
Mean Change from Baseline in the Number and Severity of Hot Flushes per Day, ITT Population, LOCF

	Number of Hot Flushes/Day (Moderate to Severe)		Severity Score/Day (Mild, Moderate, Severe)	
	Placebo n=73	EstroGel 1.25 g n=72	Placebo n=73	EstroGel 1.25 g n=72
Baseline				
Mean (SD)	11.01 (5.66)	10.33 (3.07)	2.30 (0.24)	2.36 (0.29)
Week 4*				
Mean (SD)	5.95 (5.17)	4.43 (4.13)	2.00 (0.63)	1.73 (0.73)
Mean change from baseline (SD)	-5.06 (4.91)	-5.91 (3.68)	-0.31 (0.62)	-0.63 (0.71)
Diff. vs placebo		0.85		0.32
P value†		0.019‡		0.005‡
Week 12*				
Mean (SD)	5.17 (6.52)	2.79 (3.70)	1.76 (0.84)	1.33 (0.97)
Mean change from baseline (SD)	-5.84 (4.52)	-7.55 (3.52)	-0.54 (0.84)	-1.03 (0.94)
Diff. vs placebo		1.71		0.49
P value†		0.043‡		<0.001‡

*Primary timepoint
†*P* values from Elteren's nonparametric test.
‡Statistically significantly different from placebo.

Effects on vulvar and vaginal atrophy

Results of the vaginal wall cytology showed a significant ($P \leq 0.001$) increase from baseline in the percent of superficial epithelial cells at week 12 for 1.25 g EstroGel. In contrast, no significant change from baseline was observed in the placebo group.

Transdermal effects

In 2 controlled clinical trials, application site reactions were reported by 0.6% of patients who received 1.25 g of EstroGel. Other skin reactions, such as pruritus and rash, were also noted. (See Table 4.)

Women's Health Initiative Studies

The Women's Health Initiative (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 estrogens (CE) per day alone or the use of 0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate (MPA) per day compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (nonfatal myocardial infarction (MI), silent MI, and CHD death), with invasive breast cancer as the primary adverse outcome studied. A "global index" included the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, or death due to other causes. 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 50-79; 75.3% White, 15% Black, 6.1% Hispanic, 3.5% Other), after an average follow-up of 6.8 years are presented in Table 2.

TABLE 2

Relative and Absolute Risk Seen in the Estrogen-alone Substudy of WHI

Event	Relative Risk CE vs Placebo (95% nCI*)	CE n=5310	Placebo n=5429
		Absolute Risk per 10,000 Women-Years	
CHD events†	0.95 (0.79-1.16)	53	56
Nonfatal MI†	*0.91 (0.73-1.14)*	*40*	*43*
CHD death†	*1.01 (0.71-1.43)*	*16*	*16*
Stroke‡	1.39 (1.10-1.77)	44	32
Deep vein thrombosis†§	1.47 (1.06-2.06)	23	15
Pulmonary embolism†	1.37 (0.90-2.07)	14	10
Invasive breast cancer†	0.80 (0.62-1.04)	28	34
Colorectal cancer‡	1.08 (0.75-1.55)	17	16
Hip fracture‡	0.61 (0.41-0.91)	11	17
Vertebral fractures‡§	0.62 (0.42-0.93)	11	17
Total fractures‡§	0.70 (0.63-0.79)	139	195
Death due to other causes‡‖	1.08 (0.88-1.32)	53	50
Overall Mortality‡§	1.04 (0.88-1.22)	81	78
Global index‡¶	1.01 (0.91-1.12)	192	190

*Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.
†Results are based on centrally adjudicated data for an average follow-up of 7.1 years.
‡Results are based on an average follow-up of 6.8 years.
§Not included in Global Index.
‖All deaths, except from breast or colorectal cancer, definite/probable CHD, PS or cerebrovascular disease.
¶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 alone was 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**.)

Final adjudicated results for CHD events from the estrogen-alone substudy, after an average follow-up of 7.1 years, reported no overall difference for primary CHD events (nonfatal MI, silent MI and CHD death) in women receiving CE alone compared with placebo (see Table 2).

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

For those outcomes included in the "global index," that reached statistical significance after 5.6 years of follow-up, the absolute excess risks per 10,000 person-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. (See **BOXED WARNINGS**, **WARNINGS**, and **PRECAUTIONS**.)

Results of the CE/MPA substudy, which included 16,608 women (average age of 63 years, range 50-79; 83.9% White, 6.8% Black, 5.4% Hispanic, 3.9% Other), are presented in Table 3 below.

TABLE 3
Relative and Absolute Risk Seen in the CE/MPA Substudy of WHI at an Average of 5.6 Years*

Event	Relative Risk CE/MPA vs Placebo at 5.2 Years (95% nCI†)	CE/MPA n=8506	Placebo n=8102
		Absolute Risk per 10,000 Women-Years	
CHD events	1.24 (1.00-1.54)	39	33
Non-fatal MI	*1.28 (1.00-1.63)*	*31*	*25*
CHD death	*1.10 (0.70-1.75)*	*8*	*8*
All strokes	1.31 (1.02-1.68)	31	24
Ischemic stroke	*1.44 (1.09-1.90)*	*26*	*18*
Deep vein thrombosis	1.95 (1.43-2.67)	26	13
Pulmonary embolism	2.13 (1.45-3.11)	18	8
Invasive breast cancer‡	1.24 (1.01-1.54)	41	33
Invasive colorectal cancer	0.56 (0.38-0.81)	9	16
Endometrial cancer	0.81 (0.48-1.36)	6	7
Cervical cancer	1.44 (0.47-4.42)	2	1
Hip fracture	0.67 (0.47-0.96)	11	16
Vertebral fractures	0.65 (0.46-0.92)	11	17
Lower arm/wrist fractures	0.71 (0.59-0.85)	44	62
Total fractures	0.76 (0.69-0.83)	152	199

*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).
†Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.
‡Includes metastatic and non-metastatic breast cancer, with the exception of *in situ* breast cancer.

Women's Health Initiative Memory Study

The estrogen-alone Women's Health Initiative Memory Study (WHIMS), a substudy of the WHI, enrolled 2947 predominantly healthy postmenopausal women aged 65 years and older (45% aged 65-69 years, 36% aged 70-74 years, and 19% aged 75 years and older) to evaluate the effects of conjugated estrogens (CE 0.625 mg) daily on the incidence of probable dementia (primary outcome) compared with placebo.

After an average follow-up of 5.2 years, 28 women in the estrogen-alone group (37 per 10,000 women-years) and 19 in the placebo group (25 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the estrogen-alone group was 1.49 (95% 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 estrogen plus progestin WHIMS substudy enrolled 4532 predominantly healthy postmenopausal women aged 65 years and older (47% aged 65-69 years, 35% aged 70-74 years, and 18% aged 75 years and older) to evaluate the effects of CE 0.625 mg plus MPA 2.5 mg daily on the incidence of probable dementia (primary outcome) compared with placebo.

After an average follow-up of 4 years, 40 women in the estrogen/progestin group (45 per 10,000 women-years) and 21 in the placebo group (22 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the hormone therapy group was 2.05 (95% CI, 1.21-3.48) compared to placebo.

When data from the 2 populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (93% 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**, **WARNINGS**, **Dementia**, and **PRECAUTIONS, Geriatric Use**.)

INDICATIONS AND USAGE

EstroGel is indicated in the

1. Treatment of moderate to severe vasomotor symptoms associated with menopause.
2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical 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 breast cancer
3. Known or suspected estrogen-dependent neoplasia
4. Active deep vein thrombosis, pulmonary embolism, or history of these conditions
5. Active or recent (eg, within the past year) arterial thromboembolic disease (eg, stroke, myocardial infarction)
6. Liver dysfunction or disease
7. Known hypersensitivity to ingredients in EstroGel
8. Known or suspected pregnancy. There is no indication for EstroGel 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 (eg, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (eg, personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

a. Stroke

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

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

b. Coronary heart disease

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

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

In postmenopausal women with documented heart disease (n=2763, average age 66.7 years), a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study; HERS) treatment with CE/MPA 0.625 mg/2.5 mg per day demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE/MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE/MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand three hundred 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.

c.Venous thromboembolism (VTE)

In the estrogen-alone substudy of WHI, the risk of VTE (DVT and pulmonary embolism [PE]), was reported for women receiving CE compared to placebo (30 vs 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 vs 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first 2 years. (See **CLINICAL STUDIES**

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

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

2. Malignant Neoplasms

a. Endometrial cancer

The use of unopposed estrogens in women with intact uteri has been associated with an increased risk of endometrial cancer. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk appears to be associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more, and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women taking estrogen/progestin combinations is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

b. Breast cancer

In some studies, the use of estrogens and progestins by postmenopausal women has been reported to increase the risk of breast cancer. The most important randomized clinical trial providing information about this issue is the Women's Health Initiative (WHI) (see **CLINICAL STUDIES**). The results from observational studies are generally consistent with those of the WHI clinical trial.

Observational studies have also reported an increased risk of breast cancer for estrogen-plus-progestin combination therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. For both findings, the excess risk increased with duration of use, and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping). In these studies, the risk of breast cancer was greater, and became apparent earlier, with estrogen-plus-progestin combination therapy as compared to estrogen-alone therapy. However,

these studies have not found significant variation in the risk of breast cancer among different estrogens or among different estrogen-plus-progestin combinations, doses, or routes of administration.

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

In the estrogen-plus-progestin substudy, after a mean follow-up of 5.6 years, the WHI substudy reported an increased risk of breast cancer. In this substudy, prior use of estrogen alone or estrogen-plus-progestin combination hormone therapy was reported by 26% of the women. The relative risk of invasive breast cancer was 1.24 (95% nCI, 1.01-1.54), and the absolute risk was 41 vs 33 cases per 10,000 women-years, for estrogen plus progestin compared with placebo, respectively. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 vs 25 cases per 10,000 women-years, for estrogen plus progestin compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 vs 36 cases per 10,000 women-years of estrogen plus progestin compared with placebo. In the WHI trial, invasive breast cancers were larger and diagnosed at a more advanced stage in the estrogen-plus-progestin group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the 2 groups. Other prognostic factors, such as histologic subtype, grade and hormone receptor status did not differ between the groups.

The use of estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation.

All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

3. Dementia

In the estrogen-alone Women's Health Initiatives Memory Study (WHIMS), a substudy of WHI, a population of 2947 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 4532 postmenopausal women aged 65 to 79 years was randomized to CE/MPA (0.625 mg/2.5 mg daily) or placebo.

In the estrogen-alone substudy, after an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for estrogen alone vs placebo was 1.49 (95% CI, 0.83-2.66). The absolute risk of probable dementia for estrogen alone vs placebo was 37 vs 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 CE/MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE/MPA vs placebo was 2.05 (95% CI, 1.21-3.48). The absolute risk of probable dementia for CE/MPA vs placebo was 45 vs 22 cases per 10,000 women-years.

When data from the 2 populations were pooled as planned in the WHIMS protocol, the reported overall risk for probable dementia was 1.76 (95% CI, 1.19-2.60). Since both substudies were

conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNINGS** and **PRECAUTIONS, Geriatric Use**.)

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

5. Hypercalcemia
Estrogen administration may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

6. Visual Abnormalities
Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued.

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

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 (eg, 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
Although topically administered estrogen therapy avoids first-pass hepatic metabolism, estrogens may be poorly metabolized in patients with impaired liver function. For patients with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised, and in the case of recurrence, medication should be discontinued.

5. Hypothyroidism
Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T_4 and T_3 serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid-replacement therapy. These patients should have their thyroid function monitored in order to maintain 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 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 the WHI study reported that after an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE/MPA vs placebo was 1.58 (95% nCI, 0.77-3.24) but was not statistically significant. The absolute risk for CE/MPA vs placebo was 4.2 vs 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 estrogen therapy. A few cases of malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen-alone therapy. For patients known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

10. Exacerbation of other conditions
Estrogens may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, 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 EstroGel application has not been evaluated.

12. Effect of sunscreen application
The effects of concomitant application of EstroGel and a sunscreen lotion have not been evaluated.

B. Patient Information
Physicians are advised to discuss the PATIENT INFORMATION leaflet with patients for whom they prescribe EstroGel.

C. Laboratory Tests
Estrogen administration should be initiated at the lowest dose approved for the indication and then guided by clinical response rather than by serum hormone levels (eg, estradiol, FSH).

D. Drug and 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) 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 T_3 concentrations are unaltered. Patients on thyroid-replacement therapy may require higher doses of thyroid hormone.

3. Other binding proteins may be elevated in serum (ie, corticosteroid-binding globulin, sex hormone-binding globulin , 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 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 estrogen, with and without progestin, in women, with and without an intact 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

EstroGel 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 estrogen have been identified in the milk of mothers receiving this drug. Caution should be exercised when EstroGel is administered to a nursing woman.

H. Pediatric Use

EstroGel is not indicated for use in children.

I. Geriatric Use

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

Of the total number of subjects in the estrogen-alone substudy of the WHI study, 46% (n=4943) were aged 65 years and older, while 7.1% (n=767) were aged 75 years and older. There was a higher relative

risk (CE vs placebo) of stroke in women aged less than 75 years compared to women aged 75 years and older.

In the estrogen-alone substudy of the WHIMS, a population of 2947 hysterectomized women aged 65 to 79 years was randomized to estrogen alone (CE 0.625 mg daily) or placebo. After an average follow-up of 5.2 years, the relative risk (CE vs placebo) of probable dementia was 1.49 (95% CI, 0.83-2.66). The absolute risk of developing probable dementia with estrogen-alone was 37 vs 25 cases per 10,000 women-years.

Of the total number of subjects in the estrogen plus progestin substudy of the WHI study, 44% (n=7320) were aged 65 years and older, while 6.6% (n=1095) were aged 75 years and older. There was a higher relative risk (CE/MPA vs placebo) of non-fatal stroke and invasive breast cancer in women aged 75 and older compared to women aged less than 75 years. In women aged greater than 75 years, the increased risk of non-fatal stroke and invasive breast cancer observed on the estrogen-plus-progestin combination group compared to the placebo group was 75 vs 24 per 10,000 women-years and 52 vs 12 per 10,000 women-years, respectively.

In the estrogen-plus-progestin substudy of WHIMS, a population of 4532 postmenopausal women aged 65 to 79 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 vs placebo) of probable dementia was 2.05 (95% CI, 1.21-3.48).

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

Pooling the events in women receiving CE or CE/MPA in comparison to those in women on placebo, the reported overall relative risk of 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 EVENTS

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

Because clinical trials are conducted under widely varying conditions, adverse event 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 event 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.

EstroGel 1.25 g was studied in 2 well-controlled 12-week clinical trials. Incidence of adverse events ≥5% for 1.25 g EstroGel and placebo is given below in Table 4.

TABLE 4
Incidence of Treatment-emergent Signs and Symptoms ≥5%
By COSTART Body System and by Descending Frequency of Occurrence in the EstroGel Treatment Group for the Intent-to-Treat Safety Population in 2 Well-controlled Clinical Studies
(Expressed as % of Treatment Group)

Body System/Treatment-emergent Signs and Symptoms	EstroGel 1.25 g day (n=168)	Placebo (n=73)
BODY AS A WHOLE		
Headache	20.2	17.8
Infection[*]	17.3	6.8
Pain[†]	7.1	11.0
Abdominal pain	7.7	1.4
Back pain	4.8	4.1
Flu syndrome	5.4	1.4
Asthenia	4.8	4.1
CARDIOVASCULAR SYSTEM		
Palpitations	0.6	1.4
DIGESTIVE SYSTEM		
Nausea	6.0	4.1
Flatulence	6.5	5.5
Diarrhea	4.2	0.0
METABOLIC and NUTRITIONAL SYSTEMS		
Weight gain	2.4	0.0
NERVOUS SYSTEM		
Nervousness	2.4	1.4
Depression	3.0	2.7
Anxiety	1.8	0.0
RESPIRATORY SYSTEM		
Sinusitis	3.6	1.4
Rhinitis	2.4	6.8
SKIN AND APPENDAGES		
Rash[‡]	7.1	5.5
Pruritus[‡]	4.8	2.7
Application-site reaction	0.6	0.0
UROGENITAL		
Breast pain	12.5	9.6
Metrorrhagia	3.0	0.0
Endometrial disorder[§]	1.8	1.4
Vaginitis	8.9	4.1
Pap smear suspicious[‖]	5.4	2.7
Vaginal hemorrhage	1.2	0.0

[*]Infection: upper respiratory infection, common cold, eye infection.
[†]Pain: generalized and extremity aches/pains, cramps.
[‡]Rash and pruritus: more than half of the EstroGel-treated patients who had pruritus reported itching at a body site other than the arms or reported generalized itching or itching skin. Similarly, most of the EstroGel-treated patients with rash had rash on 1 or more areas of the body in addition to the arms.
[§]Endometrial disorder: proliferative endometrium, benign endometrial disorders.
[‖]Pap smear suspicious: atypical squamous cells of undetermined significance, inflammatory changes, epithelial cell abnormality.

The following additional adverse events 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; bloating; diarrhea; dyspepsia; constipation; vomiting; abdominal cramps; cholestatic jaundice; increased incidence of gallbladder disease; pancreatitis; enlargement of hepatic hemangiomas

5. **Skin:** chloasma or melasma, which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; 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 adverse events 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

EstroGel 1.25 g is the single approved dose for the treatment of moderate to severe vasomotor symptoms and/or moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause. The lowest effective dose of EstroGel for these indications has not been determined. When prescribing solely for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.

When estrogen is prescribed for a postmenopausal woman with an intact 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 limited to the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be reevaluated periodically as clinically appropriate (eg, 3-month to 6-month intervals) to determine if treatment is still necessary (see **BOXED WARNINGS** and **WARNINGS**). For women who have an intact 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.

HOW SUPPLIED

EstroGel is a clear, colorless, hydroalcoholic 0.06% estradiol gel supplied in a non-aerosol, metered-dose pump. The pump consists of an LDPE inner liner encased in rigid plastic with a resealable polypropylene cap. Each individually packaged 93-gram pump contains 93 grams of gel and is capable of delivering 64 metered 1.25-g doses.

NDC: 0051-1028-58……..... (93-gram pump)

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].

Manufactured for:
ASCEND Therapeutics, Inc.
Herndon, VA 20170
By Laboratoires Besins International
Montrouge, France

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Utilizes EHG™ Technology

PATIENT INFORMATION
(Updated January 2007)

EstroGel®
(estradiol gel)

℞ only

Read this PATIENT INFORMATION before you start using EstroGel, and read the patient information each time you refill your EstroGel prescription. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

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

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

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

You and your healthcare provider should talk regularly about whether you still need treatment with EstroGel.

What is EstroGel?

EstroGel is a clear, colorless gel medicine that contains an estrogen hormone (estradiol) which is absorbed through the skin into the bloodstream. The estrogen hormone in EstroGel is a synthetic estrogen made from a plant source.

How is EstroGel used?

EstroGel is used after menopause for the following:

- **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 and 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 have 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 estrogens. In other women, symptoms can be more severe. You and your healthcare provider should talk regularly about whether you still need treatment with EstroGel.

- **To treat moderate to severe dryness, itching, and burning in and around your vagina**

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

Who should not use EstroGel?

Do not start using EstroGel if you have any of the following:

- **Have unusual vaginal bleeding**

- **Currently have or have had certain cancers**
  Estrogens may increase the chances of getting certain types of cancer, including cancer of the breast or uterus. If you have or have had cancer, talk with your healthcare provider about whether you should use EstroGel.

- **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 EstroGel or any of its ingredients**
  See the end of this leaflet for a list of ingredients in EstroGel.

- **Think you may be pregnant**

Talk to your healthcare provider about the following:

- **If you are breastfeeding**
  The hormone in EstroGel can pass into your breast 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 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 EstroGel works. EstroGel may also affect how your other medicines work.

- **If you are going to have surgery or will be on bedrest**
  You may need to stop taking estrogens.

How is EstroGel supplied?

EstroGel is available in a metered-dose pump that delivers 1.25 grams (g) of a gel containing 0.75 milligrams (mg) of estradiol each time the pump is depressed.

How should I use the EstroGel pump?

It is important that you read and follow these directions on how to use the EstroGel pump properly.

1. **Before using the pump for the first time, it must be primed**. Remove the large pump cover, and fully depress the pump twice. Discard the unused gel by thoroughly rinsing down the sink or placing it in the household trash in a manner that avoids accidental exposure or ingestion by household members or pets. **After priming, the pump is ready to use**, and 1 complete pump depression will dispense the same amount of EstroGel each time.
2. **Apply EstroGel at the same time each day.** 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 your EstroGel dose after your bath, shower, or sauna. If you go swimming, try to leave as much time as possible between applying your EstroGel dose and going swimming.
3. **Be sure your skin is completely dry before applying EstroGel.**
4. To apply the dose, collect the gel into the palm of your hand by pressing the pump firmly and fully with 1 fluid motion without hesitation, as illustrated.

5. Apply the gel to 1 arm using your hand. Spread the gel as thinly as possible over the entire area on the inside and outside of your arm from wrist to shoulder, as illustrated.

6. Always place the small protective cap back on the tip of the pump and the large pump cover over the top of the pump after each use.
7. **Wash your hands with soap and water after applying the gel to reduce the chance that the medicine will spread from your hands to other people.**
8. It is not necessary to massage or rub in EstroGel. Simply allow the gel to dry for up to 5 minutes before dressing.
9. **Alcohol-based gels are flammable. Avoid fire, flame or smoking until the gel has dried.**
10. Once dry, EstroGel is odorless.
11. **Never apply EstroGel directly to the breast.** Do not allow others to apply the gel for you.
12. The EstroGel 93-gram pump contains enough product to allow for initial priming of the pump twice and delivery of 64 daily doses. After you have initially primed the pump twice and dispensed 64 doses, you will need to discard the pump.

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

If someone else is exposed to EstroGel 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 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 EstroGel in my eyes?

If you get EstroGel in your eyes, rinse your eyes right away with warm, clean water to flush out any gel. 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 should I avoid while using EstroGel?

It is important that you do not spread the medicine to others, especially men and children. Be sure to wash your hands after applying EstroGel. Do not allow others to make contact with the area of skin where you applied the gel for at least 1 hour after application. **Alcohol-based gels are flammable. Avoid fire, flame or smoking until the gel has dried.**

What are the possible adverse events of estrogens?

Less common but serious adverse events include

- Breast cancer
- Uterine cancer
- Stroke
- Heart attack
- Blood clots
- Dementia
- Gallbladder disease
- Ovarian cancer

These are some of the warning signs of serious adverse events:

- Breast lumps
- Unusual vaginal bleeding
- Dizziness and faintness
- Changes in speech
- Severe headaches
- Chest pain
- Shortness of breath
- Leg pain
- Changes in vision
- Vomiting

Call your healthcare provider right away if you have any of these warning signs or any other unusual symptoms that concern you.

Common adverse events include

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

Other adverse events 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 of the possible adverse events of EstroGel. For more information, ask your healthcare provider or pharmacist.

What can I do to lower my chances of having an adverse event with EstroGel?

Talk with your healthcare provider regularly about whether you should continue using EstroGel. If you have a uterus, talk with your healthcare provider about whether the addition of a progestin is right for you. See your healthcare provider right away if you have unusual vaginal bleeding while using EstroGel. Have a breast exam and mammogram (breast x-ray) every year unless your healthcare provider tells you otherwise. 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 of getting heart disease.

Have an annual gynecologic exam.

General information about the safe and effective use of EstroGel

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

This leaflet provides a summary of the most important information about EstroGel. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about EstroGel that is written for health professionals. You can get more information by calling the toll-free number, 1-877-204-1013.

What are the ingredients in EstroGel?

EstroGel contains estradiol, purified water, alcohol, triethanolamine, and carbomer 934P.

EstroGel should be stored with the cap on securely. 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]. Do not freeze. The gel should not be used after the date printed on the end of the metered-dose pump after the term "Exp." (expiration date).

Manufactured for:
ASCEND Therapeutics, Inc.
Herndon, VA 20170
By Laboratoires Besins International
Montrouge, France

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Utilizes EHG™ Technology