CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-166

APPROVED DRAFT LABELING

500123
1E Rev 2/2004

ESTROGEL® 0.06%
(estradiol gel)

R_x only

ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER

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

CARDIOVASCULAR AND OTHER RISKS

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

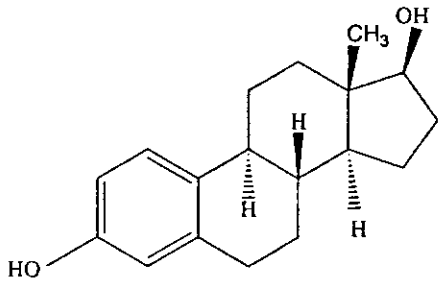
The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) relative to placebo. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)

Other doses of conjugated estrogens with medroxyprogesterone 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, 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

Percutaneous administration of ESTROGEL produces plasma concentrations of estradiol and estrone that are similar to those observed in the follicular phase of the ovulatory cycle. Typical therapeutic levels of estradiol range from 40 to 80 pg/mL for relief of vasomotor symptoms.

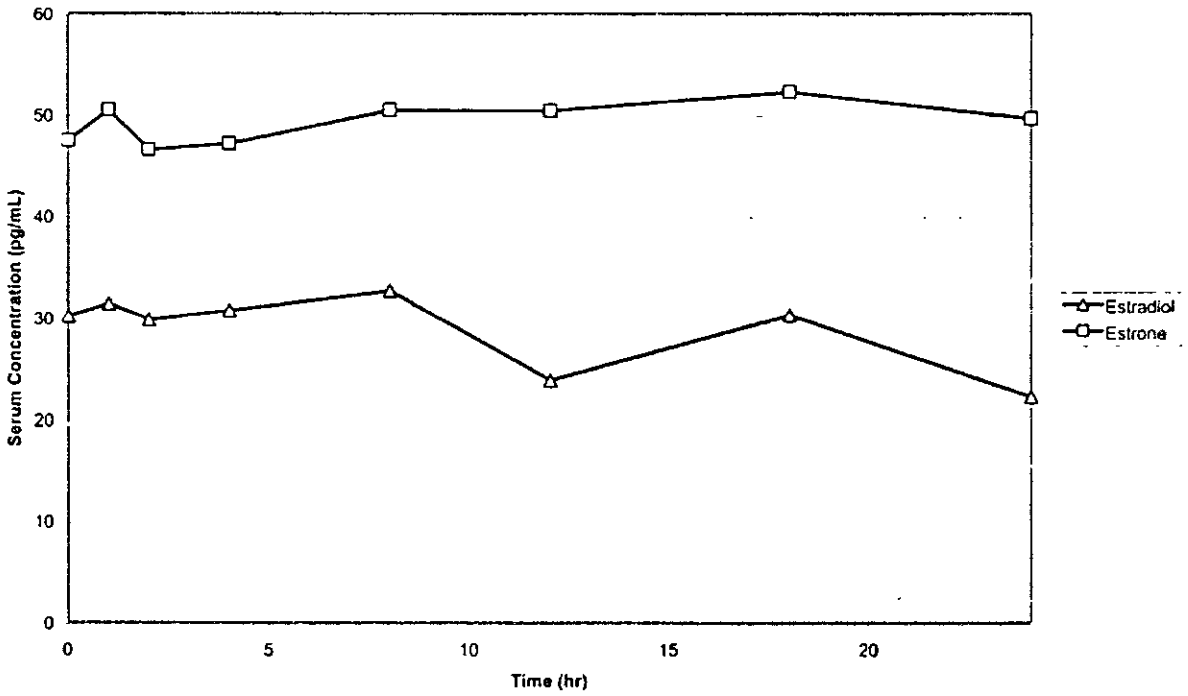
Absorption

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 on 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 one 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 concentration 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 concentrations-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.

Distribution

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

Metabolism

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

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.

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.

Drug Interactions

Drug interactions have not been assessed for 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 estrogens and may result in side effects.

Clinical Studies

Effects on vasomotor symptoms

In a placebo-controlled study, 145 postmenopausal women between 29 and 67 years of age (81.4% were Caucasian) 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 Moderate to Severe Hot Flushes Per Day, ITT Population, LOCF

	Number of Hot Flushes/Day		Severity Score/Day	
	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		0.029**		0.005**
Week 8				
Mean (SD)	5.36 (5.78)	3.44 (4.40	1.89 (0.77)	1.44 (0.90)
Mean Change from Baseline (SD)	-5.65 (4.11)	-6.89 (3.80)	-0.41 (0.78)	-0.92 (0.89)
Diff vs Placebo		1.24		0.51
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**

* p-values from Van Elteren's non-parametric test
** Statistically significantly different from placebo.
◊ Primary Timepoint

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 two 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 3.)

Estradiol Transfer

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 one arm from wrist to shoulder for a period of 14 consecutive days. On each day, one 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.

Effect of Application Site Washing

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 one hour after the application resulted in a 22% mean decrease in average 24-hour serum concentrations of estradiol.

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 equine estrogens plus 2.5 mg medroxyprogesterone acetate (MPA) per day compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome studied. A "global index" included the earliest occurrence of CHD 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 CE-only substudy is continuing and results have not been reported. The CE/MPA substudy was 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, 6.5% Black, 5.5% Hispanic), after an average follow-up of 5.2 years are presented in Table 2.

TABLE 2

Relative and Absolute Risk Seen in the CE/MPA Substudy of WHI[a]

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

[a] adapted from *JAMA*, 2002; 288:321-333

[b] includes metastatic and non-metastatic breast cancer with the exception of *in situ* breast cancer

[c] a subset of the events was combined in a "global index," defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes

[d] not included in Global Index

* nominal confidence intervals unadjusted for multiple looks and multiple comparisons

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

INDICATIONS AND USAGE

ESTROGEL is indicated in the:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.

2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of

symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.

CONTRAINDICATIONS

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

1. Undiagnosed abnormal genital bleeding.
2. Known, suspected, or history of cancer of the breast.
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. ESTROGEL therapy should not be used in patients with known hypersensitivity to its ingredients.
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 and estrogen/progestin therapy has been associated with an increased risk of cardiovascular events such as myocardial infarction and stroke, as well as venous thrombosis and pulmonary embolism (venous thromboembolism or VTE). Should any of these occur or be suspected, estrogens should be discontinued immediately.

Risk factors for arterial vascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or thromboembolism (e.g., personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

a. *Coronary Heart Disease and Stroke*: In the Women's Health Initiative (WHI) study, an increase in the number of myocardial infarctions and strokes has been observed in women receiving CE compared to placebo. These observations are preliminary and the study is continuing. (See **CLINICAL PHARMACOLOGY, Clinical Studies**.)

In the CE/MPA substudy of WHI, an increased risk of coronary heart disease (CHD) events (defined as non-fatal myocardial infarction and CHD death) was observed in women receiving CE/MPA compared to women receiving placebo (37

vs. 30 per 10,000 women-years). The increase in risk was observed in year one and persisted.

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

In postmenopausal women with documented heart disease (n = 2,763, average age 66.7 years), a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study; HERS) treatment with CE/MPA-0.625 mg/2.5 mg per day demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE/MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE/MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand three hundred and twenty-one women from the original HERS trial agreed to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE/MPA group and the placebo group in HERS, HERS II, and overall.

Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

b. *Venous Thromboembolism (VTE)*: In the Women's Health Initiative (WHI) study, an increase in VTE has been observed in women receiving CE compared to placebo. These observations are preliminary, and the study is continuing. (See **CLINICAL PHARMACOLOGY, Clinical Studies**.)

In the CE/MPA substudy of WHI, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving CE/MPA compared to women receiving placebo. The rate of VTE was 34 per 10,000 women-years in the CE/MPA group compared to 16 per 10,000 women-years in the placebo group. The increase in VTE risk was observed during the first year and persisted.

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

2. Malignant Neoplasms

a. *Endometrial Cancer:* The use of unopposed estrogens in women with intact uteri has been associated with endometrial cancer. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than one year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for 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*: Estrogen and estrogen/progestin therapy in postmenopausal women has been associated with an increased risk of breast cancer. In the CE/MPA substudy of the Women's Health Initiative (WHI) study, a 26% increase of invasive breast cancer (38 vs. 30 per 10,000 women-years) after an average of 5.2 years of treatment was observed in women receiving CE/MPA compared to women receiving placebo. The increased risk of breast cancer became apparent after 4 years on CE/MPA. The women reporting prior postmenopausal use of estrogens and/or estrogen with progestin had a higher relative risk for breast cancer associated with CE/MPA than those who had never used these hormones. (See **CLINICAL PHARMACOLOGY, Clinical Studies**.)

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

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

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

3. Gallbladder Disease

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

4. Hypercalcemia

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

5. Visual Abnormalities

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

6. 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 (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 pre-existing 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 their free thyroid hormone levels in an acceptable range.

6. ***Fluid retention.*** Because estrogens may cause some degree of fluid retention, patients with conditions that might be influenced by this factor, such as 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.*** Use of estrogen-only products, in particular for 10 or more years, has been associated with an increased risk of ovarian cancer in some epidemiological studies. Other studies did not show a significant association. Data are insufficient to determine whether there is an increased risk with combined estrogen/progestin therapy in postmenopausal women.

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 (e.g., 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, i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

4. Increased plasma HDL and 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 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

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

G. Nursing Mothers

Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Detectable amounts of estrogens 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 of age differ from younger subjects in their response to ESTROGEL.

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.

ESTROGEL 1.25 g was studied in two well-controlled 12-week clinical trials. Incidence of adverse experiences ≥5% for 1.25 g ESTROGEL and placebo is given below in Table 3.

TABLE 3

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 Two 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[a]	17.3	6.8
Pain[b]	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[c]	7.1	5.5
Pruritus[c]	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[d]	1.8	1.4
Vaginitis	8.9	4.1
Pap Smear Suspicious[e]	5.4	2.7
Vaginal Hemorrhage	1.2	0.0

[a] Infection: upper respiratory infection, common cold, eye infection.

[b] Pain: generalized and extremity aches/pains, cramps.

[c] 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 one or more areas of the body in addition to the arms.

[d] Endometrial Disorder: proliferative endometrium, benign endometrial disorders.

[e] Pap Smear Suspicious: atypical squamous cells of undetermined significance, inflammatory changes, epithelial cell abnormality.

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; 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.

8. **Miscellaneous:** Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; arthralgias; leg cramps; changes in libido; 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

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 the 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 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 limited to the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be reevaluated periodically as clinically appropriate (e.g., 3-month to 6-month intervals) to determine if treatment is still necessary (see **BOXED WARNINGS** and **WARNINGS**). For women who have a uterus, adequate diagnostic measures, such as endometrial sampling, when indicated, should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED

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

ESTROGEL is also available in a glaminate tube with a screw cap. The tube must be utilized in conjunction with an applicator to deliver the required dose. Each individually packaged tube contains 80 grams of gel and is capable of delivering 64 doses (1.25 g each).

NDC 0051-1028-58..... (93 grams Pump)
NDC 0051-1028-75.....(80 grams Tube)

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 by:
Laboratoires Besins International
Montrouge, France

Marketed by:

Unimed Pharmaceuticals, Inc.
A Solvay Pharmaceuticals, Inc. company
Marietta, GA 30062

500123
1E Rev 2/2004

PATIENT INFORMATION

(Updated February 2004)

ESTROGEL®

(estradiol gel)

R_x only

Read this PATIENT INFORMATION before you start taking 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 taking estrogens. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.

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

Using estrogens with or without progestins may increase your chances of getting heart attack, strokes, breast cancer, and blood clots. 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.

What is ESTROGEL used for?

ESTROGEL 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 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 get 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.

- **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 health care 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 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**

Tell your healthcare provider:

- **if you are breastfeeding**

The hormone in ESTROGEL can pass into your breast milk.

- **about all your medical problems**

Your healthcare provider may need to check you more carefully if you have certain conditions, such as asthma (wheezing), epilepsy (seizures), migraine, endometriosis, 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 ESTROGEL works. ESTROGEL may also affect how your other medicines work.

- **if you are going to have surgery or will be on bed rest**

You may need to stop taking estrogens.

How is ESTROGEL supplied?

ESTROGEL is available in a metered dose pump and in a tube. The metered dose pump and tube both deliver 1.25 grams (g) of a gel containing 0.75 milligrams (mg) of estradiol.

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 one 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 one fluid motion without hesitation, as illustrated.

5. Apply the gel to one 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 five 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 pump contains enough product to allow for initial priming of the pump twice and to deliver 64 daily doses. After you have initially primed the pump twice and dispensed 64 doses, you will need to discard the pump.

How should I use the ESTROGEL tube?

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

1. **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.
2. **Be sure your skin is completely dry before applying ESTROGEL.**

3. Gently squeeze ESTROGEL from the tube to fill the applicator to the halfway mark (1.25 mark). Apply the gel to one arm using the applicator. Be sure to transfer all of the gel from the applicator to the arm.
4. 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.

5. Be sure to replace the cap to the tube after each use.
6. **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.**
7. It is not necessary to massage or rub in ESTROGEL. Simply allow the gel to dry for up to five minutes before dressing.
8. **Alcohol based gels are flammable. Avoid fire, flame or smoking until the gel has dried.**
9. Once dry, ESTROGEL is odorless.
10. **Never apply ESTROGEL directly to the breast.** Do not allow others to apply the gel for you.

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 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 ESTROGEL in my eyes?

If you get ESTROGEL in your eyes, rinse your eyes right away with warm clean water to flush out any ESTROGEL. 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 one hour

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

What are the possible side effects of estrogens?

Less common but serious side effects include:

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

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

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

Call your healthcare provider right away if you get any of these warning signs, or any other unusual symptoms 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 ESTROGEL. For more information, ask your healthcare provider or pharmacist.

What can I do to lower my chances of getting a serious side effect 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 get vaginal bleeding while using ESTROGEL. Have a breast exam and mammogram (breast X-ray) every year unless your healthcare provider tells you something else. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram, you may need to have breast exams more often. If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or if you use tobacco, you may have higher chances of getting heart disease. Ask your healthcare provider for ways to lower your chances of getting heart disease.

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 800-241-1643.

What are the ingredients of 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 and the tube after the term "Exp." (expiry date).

Manufactured by:
Laboratoires Besins International
Montrouge, France

For Unimed Pharmaceuticals, Inc.
A Solvay Pharmaceuticals, Inc. company
Marietta, GA 30062-2224

500123 1E Rev 2/2004